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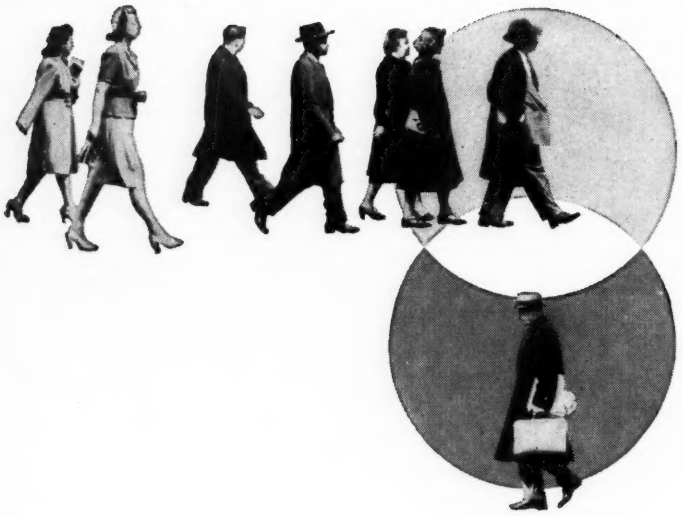

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The Journal of Allergy

VOL. 25 JULY, 1954 NO. 4

Original Articles

EFFECTS OF HISTAMINE AND EPINEPHRINE ON THE SMALL PULMONARY BLOOD VESSELS OF LIVING RABBITS

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WITH THE TECHNICAL ASSISTANCE OF PRISCILLA GORDON, AND MARY J. GRAHAM, A.B.

INTRODUCTION

THE role of histamine in allergy is still uncertain. Epinephrine has proved effective in the therapy of most types of allergic diseases. The exact mode of action of either preparation unfortunately still remains unknown. No one effort to shed further light upon these actions is likely to reveal more than one chapter of the full story. The purpose of this paper is to show the effects of both agents on the small pulmonary blood vessels of living rabbits under certain experimental conditions.

During the last fifty years, extensive experimental work aimed at determining the effects of histamine on the circulatory system has been carried out. Dale and associates[1-4] described observations in a series of experiments on living animals in which histamine was injected into a cannulated vein, while blood pressure was recorded from a cannulated artery. Dogs, cats, and monkeys showed an initial sharp fall of blood pressure, followed by a short rise, and then a slow steady drop. In rabbits, they recorded an initial blood pressure rise which later gave way to a fall. Feldberg[5] working in Dale's laboratory, however, noted an initial fall in blood pressure in the rabbit when he used chloralose anesthesia rather than urethane. He also observed narrowing of the central artery of the rabbit's pinna when histamine was given intravenously. Lewis and Grant[6-8] injected histamine into the skin of human beings and observed an initial small area of erythema, followed by a bright red flush over a larger area, and finally

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a wheal. Intravenous histamine was given to human beings by Weiss and associates.[9] In these patients during histamine injections, electrocardiograms, recordings of venous pressure, spinal pressure reading, microscopic studies of capillaries of the nail bed, arterial pressure measurements, pressures in the capillaries of the nail bed, determinations of circulating blood volume, basal metabolic rates, and red and white blood cell counts were made. They found little change in systolic arterial blood pressure, little or no change in venous pressure, no change in caliber of capillaries of nail bed, increase in basal metabolic rate, no change in the counts of the cellular elements of the blood, little change in the circulating blood volume, and an increase in the spinal fluid pressure.

Epinephrine, which is normally secreted by the medulla of the adrenal glands and plays a part in mammalian physiology, has been studied extensively for its effects on the circulatory system. Since the type of anesthesia and other experimental procedures markedly modify its actions, experimental reports are conflicting. It is not practical to review the voluminous literature here but a glance at the work of others as to its effect on the small pulmonary vessels of living mammals is called for. In 1925, Hall[10] found that 1 to 3 ml. of epinephrine, 1 to 50,000, intravenously caused a definite decrease in the size of pulmonary arterioles of living cats and rabbits. Wearn and others[11] observed with microscopes the action of epinephrine on the small pulmonary vessels of living cats and were impressed by the varied and inconstant observations. The common effects, however, were increase in linear rate of blood flow, intermittence of capillary circulation, and an increase in the number of actively flowing capillaries. After large doses, they noted a slowing, stopping, and even a reversal of the direction of blood flow. In similar experiments on cats, Macgregor[12] noted only an increase, decrease, or complete reversal of blood flow without any change in the calibers of the small pulmonary blood vessels.

MATERIALS AND METHODS

Over 200 young male rabbits were used in these experiments, only healthy animals being chosen. For anesthesia the initial intravenous dose of sodium pentobarbital was 0.04 Gm. per kilogram of body weight; further doses were administered intravenously as needed to maintain surgical anesthesia.

Only fresh preparations of histamine and epinephrine were used in these experiments. In the case of histamine, crystals of histamine diphosphate were weighed and dissolved in distilled water immediately before use. Fresh epinephrine hydrochloride, 1-1,000, was procured and diluted in distilled water just prior to intravenous injection. All preparations were injected either through a cannula in the external jugular vein or into an ear vein.

The apparatus used in these experiments was the same as that described by Irwin and Macdonald,[13] including the method of respiration without respiratory movement as well as that of transillumination of living tissue by light conducted to the under surface of the tissue by means of a fused quartz rod as reported by Knisely.[14] Also described were the quartz rod holder, experimental table, constant temperature bath, and microscopes.

Surgical techniques to expose the lungs for observation were arranged to keep hemorrhage and trauma to a minimum. The rabbit was placed on its left

side, following which a skin incision was made between the fifth and sixth ribs from the sternocostal margin to the vertebral column. The muscles of the thoracic wall were then tied and severed, and several ties were made around the fifth and sixth ribs to occlude the intercostal vessels. After the intercostal muscles were cut, the parietal pleura was incised. The fifth and sixth ribs were separated by a retractor to make an opening large enough to deliver a portion of the right lung. The exposed lung was kept moist by two gently flowing streams of mammalian Ringer's solution (NaCl 9 Gm., KCl 0.42 Gm., $NaHCO_3$ 0.5 Gm., CaCl 0.24 Gm., H_2O 1 liter) at 38° C.

The edge of the exposed lung was transilluminated for observation by a fused quartz rod with a hollow tip similar to the one described by Hoerr.[15] The lung floated on a gentle stream of mammalian Ringer's solution issuing from the tip of the rod at 38° C. at the rate of thirty drops per minute. The microscope was focused on the vessels of the edge of the dorsal surface of the exposed lung.

OBSERVATIONS

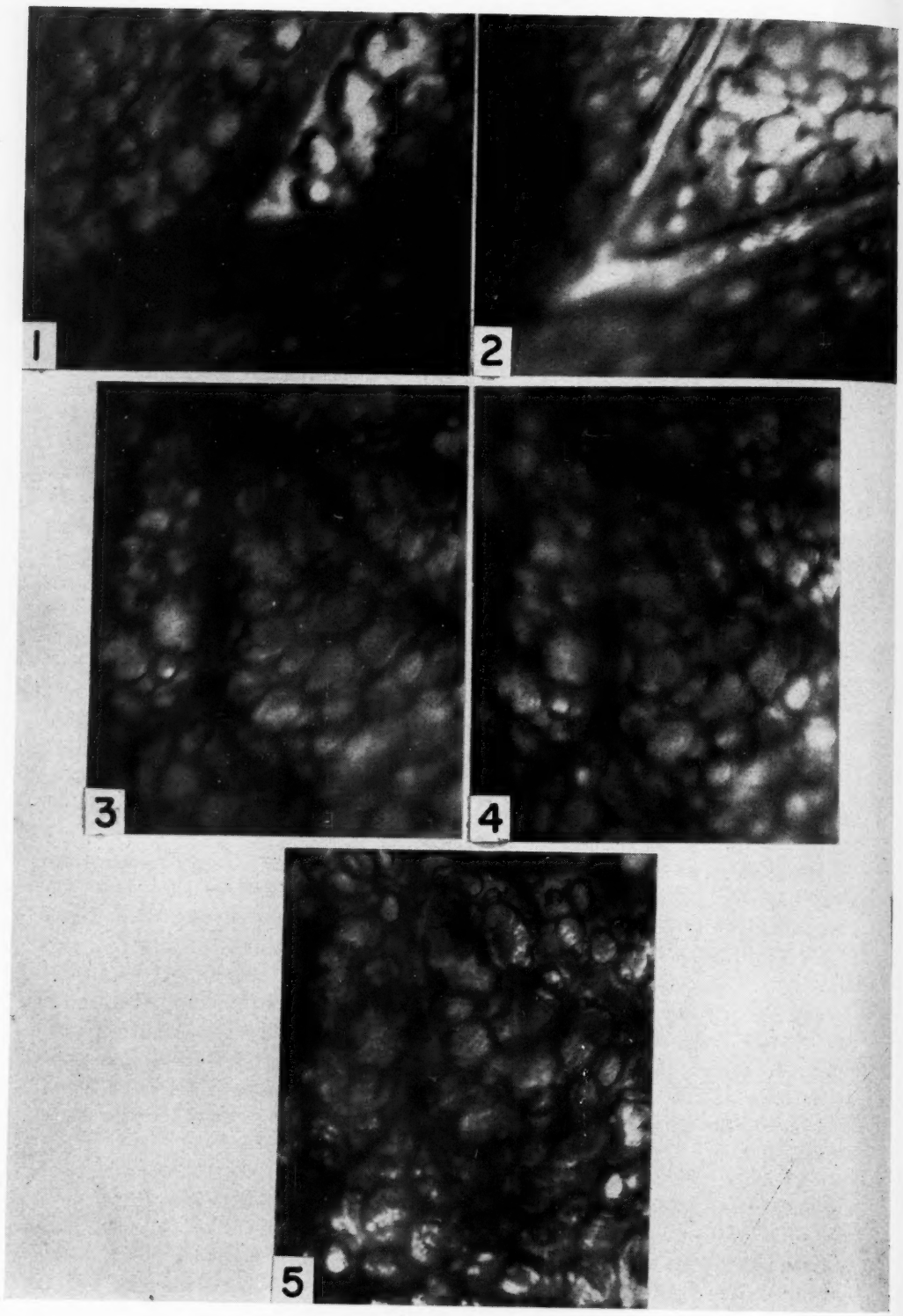
Histamine.—In a previous paper, Burrage and Irwin[16] described the small blood vessels of the living lung of rabbits before and during anaphylaxis. In the present studies, experimental conditions were similar and the normal vessels appeared as they had before.

The amount of histamine and the rate of injection may well modify its action. In these experiments, the primary interest has so far been focused on the effects of histamine given in sufficient quantity to lead to death. Under the experimental conditions described here, 8 mg. of fresh histamine per kilogram of rabbit weight given rapidly by vein generally led to death.

In microscopic observations of this type, it is possible to measure the caliber of vessels, to note the condition of the vessel walls, to determine the condition of the intravascular cellular elements, and to estimate roughly the rate of linear blood flow. In each experiment, all of the above points were considered both before and during histamine administration.

The effects of histamine on the small pulmonary blood vessels varied somewhat, but the changes in the pulmonary capillaries were very consistent. To study the effects of intravenous histamine on pulmonary capillaries, a microscopic field (200×-500×) was selected in which an alveolus had only a few open capillaries. Immediately after the histamine injection, many more capillaries opened in the same field, and those already open, dilated widely. The linear rate of flow increased at first, but this phase rapidly gave way to a slowing and finally to stagnation. The red blood cells in the capillaries formed aggregates as the rate of flow decreased. White blood cell emboli were occasionally noted. Red blood cells also permeated the capillary walls resulting in small hemorrhagic areas.

Pulmonary arterioles of various diameters ranging from 150 microns to 10 microns were studied. The size of the arterioles appeared to have little to do with the effect of histamine on them. When histamine was injected, most of the pulmonary arterioles showed at least some degree of contraction. Fig. 1 is a microphotograph illustrating a normal pulmonary arteriole, whereas Fig. 2 demonstrates the same vessel one minute after histamine. In only five experi-



Figs. 1-5. *(For legends see opposite page.)*

ments in which the rabbit died within two minutes, was no change observed in the caliber of the pulmonary arterioles. In these particular experiments, there was an abrupt cessation of linear blood flow in contrast to the usual gradual slowing which ended in stagnation. If the rabbit lived for more than two minutes after intravenous histamine, emboli were found in the arterioles. These emboli varied in composition: some obviously were white blood cell emboli, others appeared to be aggregates of red blood cells, and a few were composed of a material highly refractive to light. On occasion some of the emboli would block the lumen of arterioles. If the histamine proved nonfatal, contracted arterioles dilated and the rate of linear blood flow increased. Then the emboli disappeared.

The effects of histamine on pulmonary venules varying in caliber from 150 to 10 microns were observed. In twelve different rabbits in which death followed intravenous histamine and in which only the pulmonary venules were studied, seven animals showed constriction of pulmonary venules, four dilatation, and one no change. Fig. 3 is a microphotograph showing pulmonary venules, and Figs. 4 and 5 are the same blood vessels after histamine. Immediately after histamine, the rate of linear blood flow decreased and finally stopped altogether. In rabbits living more than two minutes after histamine, the same types of emboli as noted in the pulmonary arterioles were found. In fact emboli of all types were more numerous on the venous side.

A typical experiment will illustrate many of the above points.

Dec. 14, 1953—White male rabbit—1.1 kilograms.
1:30 P.M.—50 mg. sodium pentobarbital intravenously.
3 P.M.—Surgery completed.
3:10 P.M.—Observations on pulmonary blood vessels started.
Pulmonary arteriole, diameter 72 μ, rapid linear flow.
Pulmonary venule, diameter 85 μ, rapid linear flow.
Only a few visible capillaries, rapid linear flow.
3:13 P.M.—Rapid injection, 5 mg. histamine intravenously.
3:14 P.M.—Multiple, dilated capillaries appeared, at first rapid flow, then stasis of red blood cells in some of them.
3:15 P.M.—Same arteriole—diameter 51 μ, linear blood flow slow, multiple emboli.
3:16 P.M.—Same venule, diameter 68 μ, linear blood flow slow, multiple emboli.
3:34 P.M.—Same arteriole, diameter 74 μ, rapid linear flow, no emboli.
Same venule, diameter 80 μ, rapid linear flow, no emboli.
Same capillary network, still dilatation.
3:45 P.M.—No change from 3:34 P.M.
3:46 P.M.—50 mg. histamine, intravenously.
3:47 P.M.—No effect on arteriole, capillaries, venules.
3:50 P.M.—No effect.
4:15 P.M.—No effect.

Fig. 1.—A branching pulmonary arteriole of a rabbit.

Fig. 2.—Same arteriole as in Fig. 1, two minutes after the intravenous injection of 8 mg. of histamine diphosphate.

Fig. 3.—A pulmonary venule and its tributaries of a rabbit.

Fig. 4.—Same set of venules as in Fig. 3, one minute after the intravenous injection of 8 mg. of histamine diphosphate.

Fig. 5.—Same set of venules as in Fig. 3, three minutes after the intravenous injection of 8 mg. of histamine diphosphate. Note marked dilatation of capillaries over alveoli.

From the previous experiment it is clear that a dose of histamine about seven times the usual fatal dose failed to kill the rabbit or change the small pulmonary blood vessels once the animal had survived the initial dose. Fourteen similar experiments gave the same results. In an unanesthetized intact rabbit 5 mg. of histamine per kilogram, given intravenously, failed to kill the animal. Thirty minutes later 50 mg., intravenously failed to cause much distress in the same rabbit. It would appear that nearly fatal doses of histamine prevent subsequent huge doses from being effective.

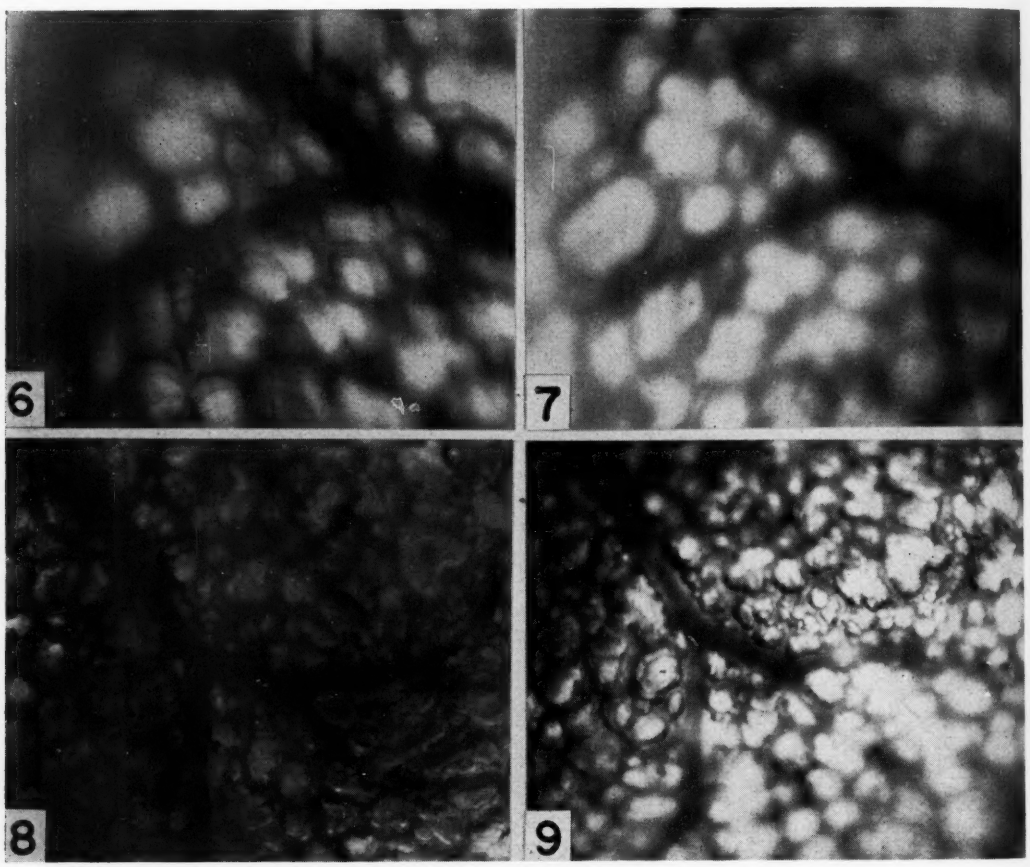


Fig. 6.—A branching pulmonary arteriole of a rabbit.

Fig. 7.—Same arteriole as in Fig. 6, thirty seconds after the intravenous injection of 0.3 ml. of 1-100,000 epinephrine.

Fig. 8.—A pulmonary venule and its tributaries of a rabbit.

Fig. 9.—Same set of venules as in Fig. 8 forty seconds after the intravenous injection of 0.4 ml. of 1-100,000 epinephrine.

Epinephrine.—Under the above experimental conditions, the effects of 0.2 to 0.9 ml. epinephrine, 1-100,000, per kilogram intravenously are fairly consistent when the rate of injection is rapid. Pulmonary arterioles varying in caliber from 150 microns to 10 microns constricted on this dose of epinephrine. Fig. 6, a microphotograph, shows a pulmonary arteriole before epinephrine, and Fig. 7

illustrates the same vessel thirty seconds after epinephrine. Within one minute the constrictor phase gave way to dilatation. During the phase of constriction the rate of linear blood flow in the pulmonary arteriole is usually markedly reduced and oscillation of blood flow is often seen. When the arteriole dilates, the flow becomes very rapid. Red blood cell aggregates were not uncommon when the arterioles were constricted, but the presence of these aggregates during the dilative phase was not noted. The effects of similar doses of epinephrine on pulmonary venules were similar to those on the arterioles. Fig. 8 is a microphotograph which shows pulmonary venules before intravenous epinephrine, and Fig. 9 shows the constriction following epinephrine.

Repeated observations of various capillary beds over alveoli were made before and after epinephrine. Visible pulmonary capillaries tended to dilate after epinephrine and, in addition, more capillaries appeared over each alveolus after epinephrine. The rate of linear flow through all pulmonary capillaries studied was markedly increased by epinephrine.

The following experiments will illustrate many of the above points.

January 11, 1954—White male rabbit—1.1 kilograms.
2 P.M.—40 mg. sodium pentobarbital intravenously.
3 P.M.—Surgery completed.
3:24 P.M.—Pulmonary vessels under observation.
3:25 P.M.—Pulmonary arteriole, diameter 80 μ, linear blood flow rapid.
3:31 P.M.—0.3 ml. epinephrine, 1-100,000, intravenously.
3:31 and 30 seconds P.M.—Same arteriole, diameter 40 μ, linear flow slow, red blood cell aggregates.
3:35 P.M.—Same arteriole, diameter 80 μ, linear blood flow rapid, a few red blood cell aggregates.
3:45 P.M.—Same pulmonary arteriole, diameter 90 μ, no aggregates of red cells, very rapid linear flow.
January 6, 1952—White male rabbit—2 kilograms.
1 P.M.—80 mg. sodium pentobarbital intravenously.
3 P.M.—Surgery completed.
3:05 P.M.—Pulmonary capillaries over one alveolus under observation.
3:09 P.M.—0.2 ml. epinephrine, 1-10,000, intravenously.
3:10 P.M.—Capillaries dilating and more capillaries visible, linear blood flow very rapid.
3:15 P.M.—Capillaries wide open, linear blood flow very rapid.
3:29 P.M.—As at 3:15 P.M.

DISCUSSION

The validity of any experimental procedure is essential for correct interpretations of results. In favor of the experimental conditions of these studies are several factors. On certain occasions, it was possible to run an experiment for over twenty-four hours, and in no instance did the pulmonary vessels show evidence of damage. Under sterile precautions, one rabbit was sewed up after observation of its small pulmonary vessels. The animal not only survived but was used again successfully in an experiment several weeks later. The blood vessels and intravascular cellular elements in over 200 rabbits showed no consistent marked changes until either histamine or epinephrine was given. After the in-

jection of either compound, the vessels and their intravascular cells reacted with a certain degree of consistency provided the dose and rate of injection were similar.

Effects of lethal doses of histamine on the small pulmonary blood vessels of living rabbits are marked. In a typical experiment, pulmonary arterioles and venules showed partial constriction, more capillaries became visible in the microscopic field, and all capillaries dilated almost as soon as the injection of histamine was completed. The linear rate of blood flow soon slowed and emboli of various types appeared within a matter of minutes. Before death, small hemorrhagic areas appeared outside the capillary walls, suggesting that the permeability of these walls had changed. Some of the emboli formed thrombi in the lumen and blocked the flow of blood through the involved vessels. Such a combination of effects must interfere with the exchange of respiratory gases and may well be an important factor in the death of these animals.

While these observations are confined to the small pulmonary blood vessels, other parts of the circulatory system are, in all probability, reacting to histamine at the same time. It may be inferred that these effects were not primarily due to the action of histamine on these blood vessels, but rather to histamine on the heart. Dale and Laidlaw,[1] however, showed that histamine had no effect on the heart itself and Lewis and Grant[6-8] demonstrated that histamine does affect minute vessels in human skin. In instances where a rabbit survived a potential lethal dose of histamine, the pulmonary arterioles and venules dilated again, normal linear blood flow was resumed, and the emboli quickly disappeared. The only lasting effect appeared to be dilation of the capillaries.

In experiments in which the rabbit died within two or three minutes after the histamine injection, the picture was somewhat different. Here there was little change in the caliber of arterioles and venules but the capillaries again showed marked dilatation. There was also an immediate cessation of linear blood flow. This rapid stoppage of blood flow is difficult to explain. It was not due to cessation of heart beat as the heart was still beating at the time. Hypothetical explanations might possibly include marked constriction of the pulmonary artery or its branches not visualized in these experiments, or marked generalized capillary dilatation throughout all the tissues.

The present experiments are obviously far too limited in scope to present more than material for tentative hypotheses rather than conclusions. The observations themselves, however, suggest that histamine's effects on the small pulmonary blood vessels are important in histamine shock. When such observations are correlated with pressure measurements of small and large pulmonary and systemic vessels coupled with microscopic observations of the small vessels of other organs during histamine shock, a more complete chapter should appear in the story of the effects of histamine on the circulatory system.

The effects of intravenous epinephrine on the small pulmonary blood vessels of living rabbits are of interest. Following an initial short period of contraction, dilatation of all vessels and a marked increase in linear rate of blood flow appear to be the dominant effects. These would at least in part overcome the changes noted during anaphylactic and histamine shock. Epinephrine definitely in-

creases the heart rate and no doubt has marked effects on other parts of the circulatory system. It is, therefore, impossible to interpret clearly these observations in regard to the total actions of epinephrine on the cardiovascular system. The initial slowing and oscillation of blood flow after epinephrine are in accord with the observations of both Wearn and associates[11] and of Macgregor.[12] The early short phase of contraction of pulmonary arterioles is similar to that observed by Hall[10] and Wearn and associates.[11]

SUMMARY

1. The actions of lethal doses of histamine on the small pulmonary blood vessels of living, anesthetized rabbits include dilatation of capillaries, contraction of arterioles and venules, the formation of emboli, and a slowing and finally stagnation of linear blood flow.

2. Epinephrine constricts the small arterioles and venules for about one minute. Dilatation follows constriction. During constriction, rate of linear blood flow is slow, but during dilatation the rate is very rapid.

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THE EFFECT OF MORPHINE ON BRONCHIAL MUSCLE

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THE deleterious effect of morphine in bronchial asthma has been remarked upon by various authors.[1, 2, 3] In 5 of 13 cases[4] of fatal asthma, morphine or Demerol was administered a few hours before death. A review by us of fatal cases of bronchial asthma at the Montreal General Hospital, occurring prior to discontinuing morphine in the treatment of bronchial asthma, showed that a high proportion received morphine or Demerol shortly before death. Since ceasing to use morphine, our results fully confirm those of Unger[5] who stated that in his experience deaths from attacks of asthma had been practically nonexistent since he abandoned the use of morphine.

The knowledge that eserine and Prostigmine may induce asthma in asthmatic subjects, but not in nonasthmatics, and the knowledge that morphine is regarded as a cholinergic drug, led us to study the effect of morphine on bronchial muscle.

Bernheim and Bernheim[6] showed that brain cholinesterase was greatly inhibited by very small concentrations of morphine and apomorphine. The results of Slaughter, Toddard, and Henderson[7] indicated that the effect of morphine on the stomach resembles that of a cholinergic drug, and that it is potentiated by Prostigmine. Wright and Sabine[8] showed that cholinesterase from human, dog, or rabbit serum, and human or rabbit brain, is inhibited by morphine, codeine, Dilaudid, and desomorphine. Slaughter and Gross,[9] in experiments on cats, obtained results which indicated that morphine depressed the cholinesterase system; and that as morphine is potentiated in its action by eserine, morphine acts as a cholinergic drug.

Scudamore, Vorhaus, and Kark[10] reported that the mean acetylcholine level in serum from 8 patients suffering from asthma was significantly greater than the mean value for healthy subjects. On the other hand, as previously reported by Milhorat,[11] and Hawes and Alles,[12] plasma and erythrocyte cholinesterase activity was found to be normal in the blood of 14 patients ill with asthma. Scudamore, Vorhaus, and Kark[10] made it clear that their observations need not mean that increased acetylcholine levels are the result of asthma.

Experiments.—Human bronchial muscle obtained from 6 patients in whom pneumonectomy or lobectomy had been performed (for carcinoma or bronchiectasis) was used. Unfortunately, none of these patients had an allergic history, or positive skin reactions to screening intradermal tests. Bronchial

From the Department of Medicine, the Montreal General Hospital and the Department of Allergy, Queen Mary Veterans' Hospital.

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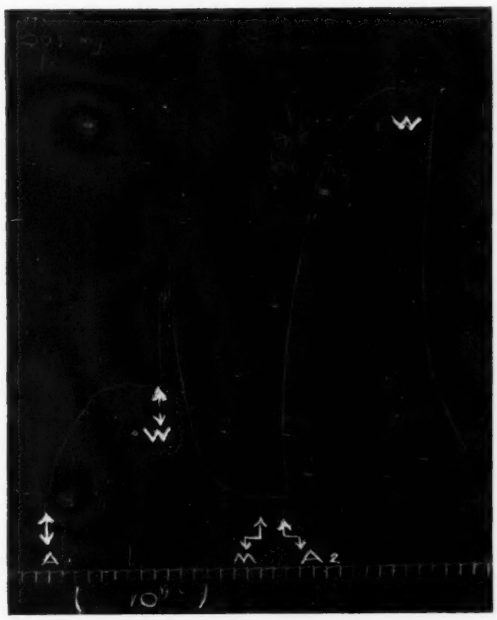

Fig. 1.—Canine bronchial chain preparation in modified Ringer's solution. Time marker one minute. Addition of acetylcholine (A) initiates muscle contraction. Preparation washed (W), and after return of resting tone morphine (M) induces no response. Acetylcholine (A_2) now induces much more powerful contraction.

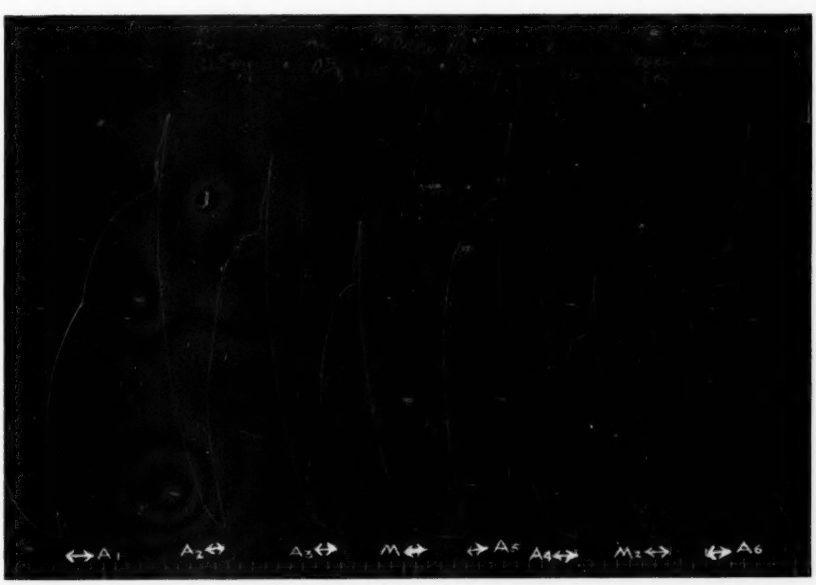

Fig. 2.—Canine bronchial chain preparation in modified Ringer's solution. Time marker one minute. The preparation has been exposed to Prostigmine. Powerful contraction follows stimulation by acetylcholine at A_1, A_2, A_3, but with decreasing intensity as Prostigmine effect wears off. At M, morphine is added to the bath. More powerful contraction follows acetylcholine at A_5. Note the absence of response to morphine alone. Simple acetylcholine response at A_4. At A_6 augmented response following morphine.

muscle from dogs was used in another series of experiments. The bronchial muscle was prepared and used in the chain technique.[13]

The human patients were all prepared preoperatively with large doses of atropine, and in several instances atropine was given during the operation. Probably on this account 3 of the human specimens reacted very feebly to acetylcholine and the remaining 3 did not react strongly. Our most active specimens, therefore, were of canine origin. In spite of the poor response of the human material, the results in 3 cases corroborated those obtained in canine specimens.

When the apparatus was arranged, viability of the muscle was established by response to acetylcholine. A series of standard contractions was recorded, washing between contractions. Then after washing, morphine was added to the bath. In none of the preparations did contraction or relaxation follow the addition of morphine up to 10 mg. per 100 c.c. If however, acetylcholine was added to the bath containing the morphine, a much stronger contraction was induced than that obtained by acetylcholine alone.

Following addition of Prostigmine to the bath, morphine alone induced no muscle response. Acetylcholine now produced a much stronger contraction.

No effect of potentiation on histamine contraction was observed from morphine.

SUMMARY

1. Morphine in the concentrations used (up to 10 mg. per 100 c.c.) had no relaxing or stimulating effect on bronchial muscle.

2. Morphine potentiates the effect of acetylcholine on bronchial muscle.

3. These findings tend to support the idea that the adverse effect of morphine in bronchial asthma may be related to an inhibitive effect of morphine on cholinesterase.

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PROLONGED CORTISONE AND HYDROCORTISONE THERAPY*

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MANY investigators[1-9] have demonstrated that cortisone will control the symptoms of various allergic manifestations in a majority of patients. However, it is the general consensus of these and other investigators that better results are obtained with ACTH. One of the possible reasons for this difference could be that corticoids other than cortisone, known to be liberated from the adrenal by ACTH stimulation, may be responsible for this. (These may be more beneficial in the relief of allergic disorders.) One of these other steroids, hydrocortisone or compound F, has recently been made available for oral administration. This substance has already proved beneficial by injection and topical application in the treatment of certain conditions of the eyes,[10] skin,[11] and joints,[12, 13] and more recently by oral therapy in rheumatoid arthritis. As yet, the effect of hydrocortisone in bronchial asthma has not been described†; hence, we wish to present our clinical evaluation of hydrocortisone and its comparative effectiveness to cortisone in the treatment of bronchial asthma.

SELECTION OF PATIENTS

Cortisone or hydrocortisone was prescribed for allergic patients only when the usually accepted methods of therapy failed to give adequate relief. Included in the "usual methods" were specific hyposensitization, other allergic management, symptomatic medications as epinephrine sprays, aminophyllin, iodides, ephedrines, etc. Asthmatic patients with acute infections were not started on the steroids, but if they had been, and developed infection, the appropriate antibiotic was prescribed and the steroid was continued.

A total of 75 patients from the allergy clinics of the Buffalo General and Children's Hospital and private practice were followed from one week to almost four years. Sixteen of these have been followed for over two years. This does not mean that these patients were receiving cortisone or hydrocortisone constantly, as there were rest periods and periods when ACTH was instituted. The actual duration of treatment with cortisone and hydrocortisone is shown in Table I.

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†Since the writing of this paper, a report[14] on this subject has just been published.

TABLE I. NUMBER OF PATIENTS AND DURATION OF TREATMENT WITH CORTISONE AND HYDROCORTISONE

DURATION OF TREATMENT	CORTISONE ALONE	HYDROCORTISONE ALONE	HYDROCORTISONE OR CORTISONE
1 week	8	3	
1 to 2 weeks	3	6	1
3 to 4 weeks	10	7	3
5 to 6 weeks	7	2	3
2 to 4 months	12	4	6
4 to 8 months	4	6	3
8 to 12 months	1		5
12 to 18 months	1		3
18 to 24 months	1		2
More than 24 months			2
Total	47	28	28

It was not found necessary to treat the infants, children, and young adults with steroids as frequently as the group over 40 years of age. Only 16 patients so treated were under 20 years of age, whereas 40 were over 40 years old (Table II).

TABLE II. AGE DISTRIBUTION OF PATIENTS TREATED WITH CORTISONE AND HYDROCORTISONE

AGES	CORTISONE	CORTISONE AND HYDROCORTISONE	TOTAL
Under 10 years	3	2	5
11 to 15	4		4
16 to 20	6	1	7
21 to 30	4	3	7
31 to 40	8	4	12
41 to 50	8	4	12
51 to 60	10	6	16
61 to 70	3	7	10
70 plus	1	1	2
	47	28	75

Of the 75 patients studied 63 were asthmatics. Twenty-three of these were given cortisone and hydrocortisone at different times.

PROCEDURE

Each selected patient was instructed as to a salt-poor diet, given supplemental potassium, either in the form of saturated solution of iodide or as potassium chloride, and was seen at least once weekly. Examinations of the chest and checking of weight and blood pressure were routine. Studies of the serum potassium, sodium, blood sugar, and eosinophil response were not carried out in this investigation. The patients were advised to continue their symptomatic medications as necessary.

DOSAGE

The initial schedule for cortisone therapy (usually in four equally divided doses) was 300 mg. the first day, 200 mg. the second day, and then 100 mg. daily for four to five days. The dosage was then gradually dropped to a level which would just keep the patient comfortable. This maintenance dosage

varied considerably with each individual and even varied in the same individual from time to time. However, the average daily maintenance dose for the adult with severe asthma was between 50 and 75 mg.

Hydrocortisone (compound F) was prescribed in a similar manner (each hydrocortisone tablet is 20 mg., whereas the cortisone tablets are 25 mg.); 240 mg. were given the first day, 160 mg. the second day, and 80 mg. daily until a maintenance level was reached. This was usually between 40 and 60 mg.

It was occasionally found that certain patients after being on maintenance therapy of either cortisone or hydrocortisone for some time would have a recurrence of symptoms; this, despite the fact that the daily dosage would be increased to as much as 100 to 200 mg. daily. In these patients the steroid would be changed from hydrocortisone to cortisone, or vice versa, and the patient was again observed. In several instances, it was found that this change in steroids would benefit the patient. It was necessary to stop both these substances and give courses of ACTH in 23 of the 63 asthmatics studied. After courses of ACTH, or rest periods without any hormone therapy, patients would often respond again.

The comparative efficacy of cortisone and hydrocortisone in allergic rhinitis, nasal polyposis, urticaria, atopic dermatitis, periarteritis, and disseminated lupus erythematosus was also noted. Twelve patients studied, in addition to their asthma, had concomitant severe allergic rhinitis and nasal polyps. One other patient, without bronchial asthma, but with allergic nasal symptoms, was treated with cortisone.

RESULTS

The clinical evaluation of drugs in so variable a condition as bronchial asthma is very difficult. The data presented are clinical impressions based on physical examination, subjective symptoms, and the amount of symptomatic medication the patients used for relief. Of the 63 patients under cortisone therapy, 41 (65 per cent) had very satisfactory improvement (Table III). Only 23 of these 63 patients had hydrocortisone at different times and 15 (65 per cent) of them were benefited. In this limited group of patients, it was noted that 4 of these 23 patients obtained better relief with cortisone than hydrocortisone, whereas 7 preferred hydrocortisone. Twelve of these patients obtained equal relief from each.

TABLE III. EFFECT OF CORTISONE AND HYDROCORTISONE ON BRONCHIAL ASTHMA

	NUMBER OF CASES	POOR	FAIR	GOOD	EXCELLENT
Cortisone	63	7	15	39	2
Hydrocortisone	23	3	5	15	

		CORTISONE BETTER	HYDROCORTISONE BETTER	EQUAL
	23	4	7	12

Eight of the 13 patients with allergic rhinitis and nasal polyps treated with cortisone had definite improvement—whereas 5 of 6 such patients were

markedly aided by hydrocortisone (Table IV). Of the 6 patients who received both compound F and compound E at different times, 4 found both substances to be similarly effective, but 2 obtained better results on hydrocortisone.

TABLE IV. EFFECT ON ALLERGIC RHINITIS AND NASAL POLYPS

	NUMBER OF CASES	POOR	FAIR	GOOD	EXCELLENT
Cortisone	13	2	2	8	1
Hydrocortisone	6		1	4	1

		CORTISONE BETTER	HYDROCORTISONE BETTER	EQUAL
	6	0	2	4

Only 5 patients with chronic urticaria were followed. One of 3 had relief from cortisone, and 2 additional patients failed completely to respond to adequate doses of either cortisone or hydrocortisone. On the other hand, 3 patients with neurodermatitis responded well to cortisone. One patient with a generalized eruption following a dermatitis venenata failed to respond to cortisone, but did remarkably well on oral hydrocortisone even in smaller dosages.

One patient with periarteritis nodosa and bronchial asthma has been on intermittent steroid therapy for almost four years. In this person lower dosages of hydrocortisone than cortisone are needed for maintenance therapy.

Disseminated lupus erythematosus in a 44-year-old man was kept under better control by cortisone than by hydrocortisone—but eventually neither of these hormones were of value.

SIDE EFFECTS

The usual side effects or hyperphysiologic responses to these steroids were encountered (Table V). The most frequent ill effect was edema, this despite

TABLE V. SIDE EFFECTS

	CORTISONE	HYDROCORTISONE
Edema	11	2
Acne	2	
Moon facies	4	0
Insomnia	4	2
Bloating	3	1
Nervousness	1	
Palpitation		1
Abdominal pain	3	
Anorexia	1	1
Diarrhea	1	
Nausea	2	
Emesis	1	1
Skin rash	1	
Nocturia	1	
Asthma worse	1	1
Perspiration	2	
Weakness, numbness, and fainting	1	
Sore throat	1	

	NUMBER OF PATIENTS	NUMBER OF PATIENTS WITH SIDE EFFECTS	PERCENTAGE OF SIDE EFFECTS
Cortisone	75	24	32.0
Hydrocortisone	28	6	21.4

low-sodium diets and supplemental potassium. In this relatively small group of patients, the incidence of these side effects appeared lower with hydrocortisone than cortisone. This probably could be attributed to the lower dosage schedule for the compound F, but the difference is not statistically significant.

DISCUSSION

The fact that ACTH, cortisone, and now hydrocortisone are useful tools in the symptomatic management of the severe allergic individual has been definitely established. The evidence presented here indicates that this method of therapy can be carried out on a long term basis without ill effects, provided the usual care and precautions are followed.

One of the most difficult groups of severe intractable asthmatics to keep comfortable are those who are sensitive to aspirin. They usually have associated recurrent nasal polyps and sinusitis. Eight such aspirin-sensitive asthmatics were followed for two years or more on steroid therapy. All but one obtained relief with these various forms of steroid—HP ACTHAR Gel (Armour), cortisone, or hydrocortisone, but not necessarily with all three (Table VI). Three of these patients complained of aggravation of their asthmatic states, with constriction in the chest, wheezing, palpitation, and bloating within fifteen minutes after the ingestion of hydrocortisone tablets. However, on subsequent oral administration at a later date, 2 of the patients could tolerate and did obtain benefit from compound F.

TABLE VI. EFFECT ON BRONCHIAL ASTHMA IN ASPIRIN-SENSITIVE PATIENTS TREATED WITH ACTH, CORTISONE, OR HYDROCORTISONE (DEGREE OF RELIEF)

PATIENT	ACTH	CORTISONE	HYDROCORTISONE
T. K.	++++	++	++
G. B.	++++	0	0
J. D.	+++	+++	+++
R. G.	+++	+++	+++
A. R.	+++	++	++
A. Z.	0	0	−
G. E.	−	+++	−
R. B.	−	+++	−

More important than the choice of either cortisone or hydrocortisone in the management of allergic individuals is the dosage level. Maintenance therapy with these steroids, to be successful, must be carefully regulated for the minimal *effective* daily dose in each individual. (A patient whose dosage is below his adequate needs, would not respond to either steroid at that level.)

Patients on long-term therapy with either cortisone or hydrocortisone should be given rest periods from these hormones. Continued therapy could conceivably produce atrophy of the adrenal glands, and it therefore might be wise to stimulate these adrenals with a few injections of ACTH every few months.

SUMMARY AND CONCLUSIONS

1. Cortisone and now hydrocortisone have been used for prolonged treatment of allergic disorders with adequate success.

2. Hydrocortisone is at least equally effective to cortisone in the relief of bronchial asthma.

3. The comparable effective dose of hydrocortisone is approximately two-thirds that of cortisone.

4. The proper maintenance level of dosage is more important than the choice between cortisone and hydrocortisone.

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COMPARATIVE RESULTS OF THE USE OF ACTH, CORTISONE, AND HYDROCORTISONE IN THE TREATMENT OF INTRACTABLE BRONCHIAL ASTHMA AND PULMONARY EMPHYSEMA

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WITH THE TECHNICAL ASSISTANCE OF SYLVIA ITKIN

EARLY reports on the efficacy of ACTH and cortisone in the treatment of bronchial asthma and pulmonary emphysema of the bronchospastic type indicated that partial or complete relief of bronchospasm could be expected in 75 to 80 per cent of the cases treated,[1-6] with recurrence of symptoms one to three weeks after cessation of therapy.[7-15] During the past 4 years, the authors have had an opportunity to follow the clinical course of 107 patients suffering from chronic intractable asthma and 56 patients with severe pulmonary emphysema who were treated with one or more trials of corticotropin, cortisone, hydrocortisone, or combinations of these agents. The diagnosis of pulmonary emphysema was substantiated by x-ray evidence of hyperradiability of the lungs, fluoroscopic observation of diminished diaphragmatic excursion, and in some instances measurement of the residual volume. Certain tentative opinions concerning the use of these hormones in bronchospastic respiratory disease have been formulated as a result of this study.

TABLE I. THREE HUNDRED AND NINE COURSES OF ACTH, CORTISONE, AND HYDROCORTISONE ADMINISTERED TO 163 PATIENTS WITH BRONCHOSPASTIC PULMONARY DISEASE: AGE AND SEX DISTRIBUTION

	ACTH		CORTISONE		HYDROCORTISONE	
	NUMBER OF CASES	NUMBER OF COURSES	NUMBER OF CASES	NUMBER OF COURSES	NUMBER OF CASES	NUMBER OF COURSES
Bronchial asthma	45	96	41	87	21	34
Pulmonary emphysema	22	34	20	36	14	22
Total	67	130	61	123	35	56
Bronchial asthma						
Age: Mean (yr.)	47.7		50.1		43.9	
Sex: Male	19		19		10	
Female	26		22		11	
Pulmonary emphysema						
Age: Mean (yr.)	62.3		60.2		61.4	
Sex: Male	16		14		11	
Female	6		6		3	

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Approximately half of the 163 patients were treated on an ambulatory basis while the remainder were hospitalized. There were 89 men and 74 women in this series ranging from 11 to 78 years of age. The courses of ACTH, cortisone, and hydrocortisone administered are shown in Table I. Although there were fewer patients treated with hydrocortisone than with either ACTH or cortisone, all groups were comparable as to age, sex, and the severity and duration of the disease process.

All the patients were placed on a salt-poor diet and received 1 Gm. of enteric-coated potassium chloride three times daily during the period of administration of ACTH or the steroid hormones. Approximately 55 per cent of the patients, comprising the majority of the emphysema subjects together with selected numbers of the asthma group who gave evidence of some degree of water and salt retention, were given a mercurial diuretic during treatment.

ACTH-Treated Patients.—Corticotropin* was administered in dosages of 25 mg. intramuscularly every 6 hours for 4 to 5 days in the majority of the patients treated. In ten instances, 50 mg. were given at 6-hour intervals for the first two injections. Twenty-five of the courses consisted of 60 mg. of Acthar Gel given once daily for a period of 5 to 6 days with 50 mg. of corticotropin added to the first two injections.

Of the 130 courses of ACTH, 43 per cent resulted in a complete remission with absence of bronchospasm, elimination or marked reduction in expectoration, and a striking increase in exercise tolerance; 39 per cent showed a partial remission and 18 per cent resulted in no improvement. This is summarized in Table II. It was noted that patients with uncomplicated bronchial asthma experienced the best response, while those subjects with an underlying emphysema exhibited for the most part only a partial remission.

TABLE II. DOSAGE AND EFFECT OF ACTH EMPLOYED IN THE TREATMENT OF BRONCHIAL ASTHMA OR PULMONARY EMPHYSEMA

	NUMBER OF COURSES	DAILY DOSE AVERAGE (MG.)	DAYS TREATED		REMISSIONS			
			AVERAGE	RANGE	COMPLETE	PARTIAL	NONE	DURATION* AVERAGE (DAYS)
					(PER CENT)			
Bronchial asthma	96	75	5.3	3-8	49	32	19	16.5
Pulmonary emphysema	34	80	4.7	3-10	26	59	15	14.8
Total	130				43	39	18	

*Twelve patients with remissions of more than two months' duration were excluded.

The average duration of remission for the patients with bronchial asthma and pulmonary emphysema was 16.5 days and 14.8 days, respectively. Nine subjects with asthma and 3 with pulmonary emphysema had remissions of more than 2 months. One patient remained free of asthma for 1 year, while the longest remission in pulmonary emphysema was 3.3 months. Since it is exceedingly difficult to evaluate these prolonged remissions in terms of drug

*Supplied by Armour Laboratories under the trade name of Acthar.

therapy or the superimposition of a spontaneous remission, the data compiled in these patients were excluded from the calculations on average duration of remission following ACTH.

Adverse reactions to adrenocorticotropic hormone were encountered in 15 per cent of the 130 courses administered. For the most part, these reactions were of minor importance, and were characterized by signs of mild hyperadrenalism, such as "mooning" of the facies and a slight increase in fat deposition about the pelvis. Significant fluid retention occurred in 5 patients; 2 of these with advanced emphysema who failed to restrict their salt intake exhibited acute pulmonary congestion. In one patient, a mild transient depressive state was observed. An anaphylactoid type of reaction occurred in 3 patients at the onset of their second course of ACTH characterized by severe dyspnea, cyanosis, and confusion of consciousness. Two of these patients had relief within one hour after the administration of adrenalin, while, in the third, immediate disappearance of symptoms followed a subsequent intravenous injection of 50 mg. of Benadryl. In 2 patients, an initial dose of ACTH was followed by signs of increased asthma within a period of 15 minutes. One of these subjects subsequently received a full course without further incident. In the second patient, recurrence of severe asthma after two succeeding injections necessitated the abandonment of this form of treatment.

The presence of an underlying chronic paranasal sinus or bronchopulmonary infection was the apparent cause of failure to respond to ACTH in 6 patients. The development of purulent expectoration accompanied by an increase in dyspnea and a low-grade fever prompted the administration of antibiotics in conjunction with adrenocorticotropic hormone in these instances.

Cortisone-Treated Patients.—Thirty-eight of the 123 courses of cortisone acetate were administered by intramuscular injection in dosages of 300 mg. daily for the first 2 days, 200 mg. daily for 3 additional days, and 100 mg. daily from the sixth to the tenth day. The remaining 85 courses were prescribed with the oral* preparation in dosages of 100 mg. every 6 hours for the first 3 days, 50 to 75 mg. at 6-hour intervals for 3 days followed by 100 mg. daily in 4 equal doses for an additional 4 days.

A complete clinical remission was obtained in 59 per cent of the 123 courses of cortisone. Twenty-seven per cent were only partially benefited and 14 per cent of the courses resulted in failures. This is summarized in Table III. As

TABLE III. CORTISONE DOSAGE AND RATE OF REMISSION IN THE TREATMENT OF BRONCHIAL ASTHMA AND PULMONARY EMPHYSEMA

	NUMBER OF COURSES	DAILY DOSE AVERAGE (MG.)	DAYS TREATED		REMISSIONS			DURATION* AVERAGE (DAYS)
			AVERAGE	RANGE	COMPLETE	PARTIAL	NONE	
					(PER CENT)			
Bronchial asthma	87	210	8.8	3-21	68	22	10	15.5
Pulmonary emphysema	36	200	9.0	3-15	39	39	22	12.6
Total	123				59	27	14	

*Nine patients with remissions of more than two months' duration were excluded.

*Supplied by Merck & Co., under the trade name of Cortone.

with corticotropin, the most gratifying results were obtained in patients with uncomplicated bronchial asthma, 68 per cent of whom responded with a complete remission as compared to 39 per cent for the patients with pulmonary emphysema.

The average duration of remission for the patients with bronchial asthma and pulmonary emphysema was 15.5 days and 12.6 days, respectively. Nine patients with bronchial asthma were completely symptom-free for periods of 2 to 7 months while the longest remission in the group with emphysema was 43 days. These cases have been excluded from the calculation of the average duration of remission since it was felt that they represented an unusual response to the drug. Patients with bronchospasm due to specific inhalants such as pollen, and those in whom a state of intractable asthma was precipitated by an upper respiratory infection consistently responded with longer remissions than the patients in whom a chronic asthmatic state was present, independent of any obvious exciting cause, but believed to be related to bacterial hypersensitivity.

The common side effects of mild hyperadrenalism and fluid retention were encountered in 16 members of this group. Only one patient who had received 10 courses of cortisone showed a well-defined increase in fat deposition about the hips and a "mooning" of the face. Four patients who complained of epigastric pain and nausea, with no objective evidence of peptic ulcer, responded to aluminum hydroxide gel. There were two instances of thrombo-embolic phenomena. One patient with pulmonary emphysema had received 4 days of adrenocorticotropic hormone without benefit. On the third day of cortisone therapy, he developed the classical signs of pulmonary infarction. The second patient had a thrombophlebitis of the right lower extremity on the twelfth day of cortisone administration. Both responded well to anticoagulant therapy. In 12 of the 17 courses listed as unsuccessful, the reactivation of a chronic bronchopulmonary or sinus infection was presumed responsible, since increase in cough and the appearance of a grossly purulent sputum were observed during cortisone therapy. In two patients, acute fulminating pansinusitis with chemosis and painful swelling of the face necessitated interruption of therapy. Antibiotic therapy and surgical drainage were followed by a sustained partial remission. A significant elevation in blood pressure, 20 mm. Hg or more systolic, was noted in 5 cases without any evidence of circulatory failure. These patients had received potassium chloride and mercurial diuretics during the period of cortisone administration.

A feeling of well-being bordering on euphoria associated with a remarkable increase in appetite was observed in the majority of the cortisone-treated patients. The disappearance of this characteristic euphoria upon termination of therapy was disappointing to the majority of the patients, but in no instance did a frank depression supervene. Two subjects complained of increased nervous tension to the point of agitation and insomnia. In all, there was an incidence of 29 per cent of adverse reactions during the 123 courses of cortisone.

Death occurred in one patient with a history of chronic intractable asthma of 12 years' duration. Repeated courses of corticotropin and cortisone were resorted to in an effort to ameliorate continuous episodes of status asthmaticus

during 1951 with diminishing responsiveness to these hormones. Maintenance therapy with 50 to 75 mg. of cortisone daily for a three-month period resulted in slight improvement with gradual relapse. Within 24 hours after discontinuing cortisone therapy, severe bronchospasm ensued accompanied by marked delirium, hyperpyrexia, and a shocklike state. Despite combined cortisone and intravenous ACTH therapy plus supportive measures, the patient expired 48 hours after admission with the clinical picture of an "Addisonian-like crisis."

Two additional patients with pulmonary fibrosis had severe flare-ups of dyspnea, muscular weakness and pain, and fever following termination of cortisone therapy. Immediate improvement took place on resumption of therapy.

Hydrocortisone-Treated Patients.—Fifty-six courses of hydrocortisone* were administered orally to 35 patients employing two treatment schedules depending upon the severity of the disease process. In status asthmaticus and advanced pulmonary emphysema associated with bronchial obstruction, 50 mg. of hydrocortisone were given at 6-hour intervals for the first two days. This dose was lowered to 40 mg. every 6 hours for the next two days, followed by 100 mg. daily in divided doses for 6 days. In the less severe bronchospastic states, a daily dose of 160 mg. was administered in 4 equal doses for the first 4 days. This was reduced to 80 mg. per day for the next 6 days. In general, the average total dose of hydrocortisone was 50 to 60 per cent of the cortisone dosage employed in the preceding series.

As illustrated in Table IV, complete remissions resulted in 66 per cent of the 56 courses administered. Thirty per cent had partial relief of dyspnea and wheezing, while 4 per cent showed no improvement. Qualitatively, the variation in response to hydrocortisone therapy between patients with intractable bronchial asthma and the bronchospastic type of pulmonary emphysema was similar to that encountered with ACTH and cortisone. The average duration of remission, however, was somewhat longer, averaging 18.4 days for the asthmatic patients and 20.5 days for the emphysema group. Only one patient had a remission exceeding 3 months.

TABLE IV. HYDROCORTISONE DOSAGE AND RESULTS OF THERAPY IN PATIENTS WITH BRONCHIAL ASTHMA OR PULMONARY EMPHYSEMA

	NUMBER OF COURSES	DAILY DOSE AVERAGE (MG.)	DAYS TREATED		REMISSIONS			
			AVERAGE	RANGE	COMPLETE (PER CENT)	PARTIAL (PER CENT)	NONE (PER CENT)	DURATION* AVERAGE (DAYS)
Bronchial asthma	34	110	9.5	3-14	73	24	3	18.4
Pulmonary emphysema	22	110	9.0	4-10	55	41	4	20.5
Total	56				66	30	4	

*Excluding one patient with a remission of over three months' duration.

The 8 per cent incidence of adverse effects due to hydrocortisone was significantly lower than with ACTH or cortisone. In addition, the reactions

*Supplied by Merck & Co. under the trade name of Hydrocortone.

in 3 of the 4 instances were mild in character and only one patient discontinued therapy because of insomnia and severe excitation. The adverse reactions to ACTH and the steroids encountered in this study are listed in Table V.

TABLE V. COMPARISON OF THE ADVERSE REACTIONS TO ACTH, CORTISONE, AND HYDROCORTISONE ENCOUNTERED IN 309 COURSES OF THERAPY IN BRONCHIAL ASTHMA AND PULMONARY EMPHYSEMA

	ACTH	CORTISONE	HYDROCORTISONE
Hyperadrenalism (rounding of facies, fat deposition, hirsutism, mild hypertension)	1	8	1
Fluid retention	5	8	
Mental symptoms: Depression	1	1	1
Excitation		2	2
Activation of infection	6	12	
Miscellaneous: Abdominal pain, nausea	1	1	
Psoriasis (exacerbated)	1		
Headache	1	3	
Sneezing		1	
Thrombo-embolism	1	2	
Anaphylactoid reaction	3		
Total	20	38	4
Incidence (per cent)	15	29	8

Although it is fully appreciated that each patient should be observed carefully and the dose of ACTH or steroid regulated according to the individual requirement, experience with a large group of ambulatory clinic patients resulted in the uniform treatment schedules employed in the present series. In 20 preliminary trials, smaller initial dosages of cortisone, 100 to 150 mg. daily, resulted in only partial remissions with an appreciable delay of 7 to 9 days before any improvement was apparent.

Ventilatory function studies including vital capacity, resting ventilation breathing air and oxygen, and maximum breathing capacity were carried out in selected members of each group. All gradations of improvement were noted; but since these tests revealed no change, either qualitatively or quantitatively, from the remissions induced by means other than ACTH or the steroids, they are not presented. The complete study of one patient with periarteritis nodosa accompanied by severe intractable bronchospasm, treated with both corticotropin and cortisone, has been reported previously.[15]

The disappointingly short duration of remission encountered in the majority of the patients treated afforded an opportunity to compare the results of multiple short courses of therapy and a program of continuous maintenance therapy.

Multiple Course Therapy.—Seventy-two patients of the entire series received two or more courses of ACTH or steroid therapy. In each instance, the dosage of hormone and interval of therapy were identical with the initial course. It was of interest, therefore, to compare the response in such subsequent courses with the initial effect. This is illustrated graphically in Fig. 1. Whereas 68 per cent of the 31 subjects had an excellent remission to the initial course of ACTH, only 27 per cent responded in a similar fashion to subsequent courses. Of the 25 patients receiving cortisone, 80 per cent had a complete remission

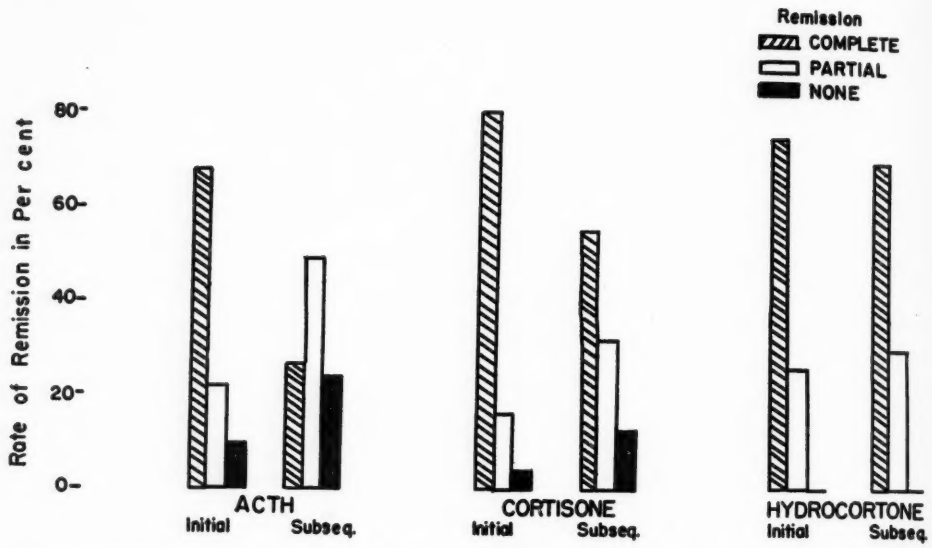

Fig. 1.—Comparison of response to initial and subsequent courses of steroid therapy in 72 patients with bronchospastic pulmonary disease.

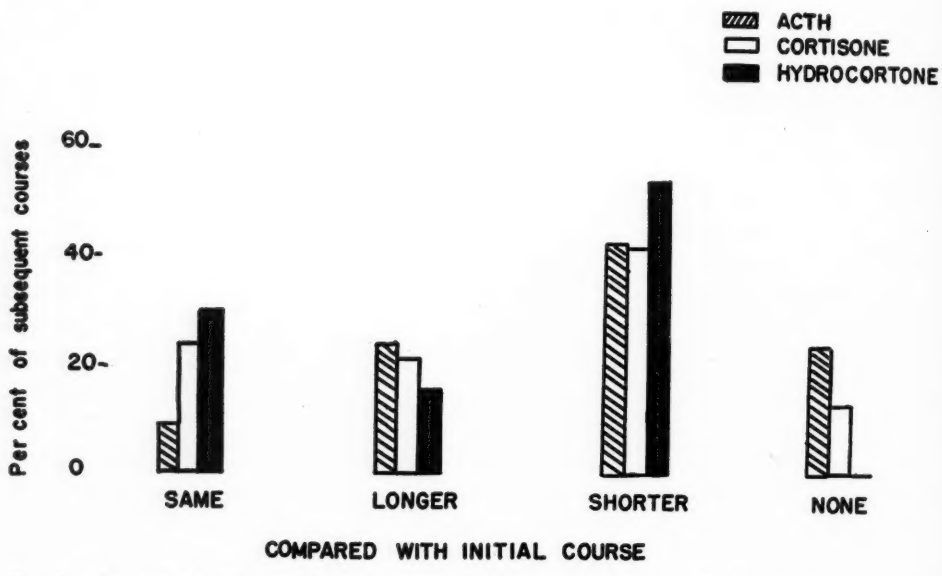

Fig. 2.—Comparison of duration of remission induced by initial and subsequent courses of steroid therapy.

with the first course, as contrasted to 55 per cent on subsequent courses. This difference is insignificant in the 16 patients treated with hydrocortisone; 75 per cent showing excellent response to the initial course and 70 per cent having the same response to subsequent courses. In addition, over half the entire series responded with a shorter duration of remission as compared with that of the initial course (Fig. 2). The effect of multiple courses of ACTH appeared to be significantly different from the steroids in that 24 per cent of the patients had no alleviation of symptoms on subsequent trials.

Maintenance Therapy for Severe Chronic Bronchospasm.—While ACTH, cortisone, and hydrocortisone were exceedingly useful in tiding the seriously ill patient over an acute episode of bronchospasm, the remissions induced by these agents were characteristically short-lived in those patients suffering from the chronic form of severe intractable asthma. Some form of maintenance therapy appeared desirable in order that the effect of a period of prolonged symptomatic improvement on the activity of the disease process could be better evaluated. Those patients who relapsed shortly after withdrawal of ACTH or the steroids and who continued to remain refractory to the ordinary measures designed to relieve bronchospasm were placed on maintenance programs as follows: (1) Twenty-three patients who had received a 10-day course of oral cortisone were given follow-up injections of 60 units of ACTH gel at weekly intervals. A partial remission of 2 to 3 months' duration was maintained by this program in 15 members of this group. One woman, receiving ACTH gel every 6 to 9 days, has maintained her improvement over 10 months with slight hirsutism and mooning of the facies as the only indication of prolonged therapy. (2) Twelve patients, following an initial course of cortisone, received 400 mg. of oral cortisone on one day of each week. In 5 patients, some prolongation of the remission, up to 6 weeks, occurred; but for the group as a whole no significant improvement was maintained. (3) At the present writing, 30 patients have been followed for periods of 9 to 24 months on small daily doses of oral cortisone or hydrocortisone, ranging from 20 to 75 mg. daily in divided doses. During this period, clinically satisfactory remissions have been maintained in 21 patients with a minimum of adverse reactions. One woman gained 40 pounds over a 7-month period which was attributed to increased fat deposition and not water retention. In 4 other individuals cortisone "escape" has occurred on several occasions following the exacerbation of a chronic sinobronchitic infection. Appropriate antibiotic therapy and increase of the cortisone dosage to 200 mg. daily for several days re-established the remissive state. Bilateral pulmonary tuberculosis developed in one patient who took cortisone over a 3-month period against advice. Further comment on this occurrence will be found later. Discontinuance of cortisone in 6 patients resulted in a gradual relapse occurring over a 2- to 3-week period.

In 2 patients with pulmonary fibrosis significant relief of dyspnea and cough has been maintained for a period of 3 months on 100 mg. of cortisone daily. Omission of the drug for a period of 4 days resulted in a reappearance

of severe dyspnea accompanied by cough and crepitant râles over both lung fields. Unsatisfactory control of bronchospasm occurred in 9 of the 30 cases on this type of maintenance therapy.

COMMENT

A comparison of the effect of ACTH, cortisone, and hydrocortisone in the treatment of intractable bronchial asthma and pulmonary emphysema would seem to indicate that a greater percentage of the patients treated with the steroids had a complete remission as contrasted with the ACTH group. However, when correction was made for the variations in response to multiple course therapy, there appeared to be no significant difference in the character of the remission induced by either ACTH, cortisone, or hydrocortisone. Although the onset of clinical improvement with corticotropin was found, at first, to be more rapid than with cortisone, the use of larger initial dosages of cortisone made this difference much less marked. In the majority of cases, relief of bronchospasm first became manifested in 24 to 48 hours after the administration of ACTH as compared with a lag of 4 to 5 days with cortisone. One of the very striking features of this study was the almost immediate response to hydrocortisone, occurring as it did within 18 to 36 hours after the onset of therapy.

Rosenberg and associates[16] found that the remissions induced by repeated courses of corticotropin were usually of the same duration in the same patient. In addition, he reported no difference in the effects of an abrupt cessation of ACTH therapy from a gradual tapering off, although the latter method was considered preferable. Our findings are in agreement with other investigators[5, 8, 14] who reported that the response to subsequent courses was frequently not as good as with the initial course. A tendency for asthmatic symptoms to recur more quickly, i.e., shortening of the remission period, after successive courses, was noted in the majority of the patients in the present series. Furthermore, our own experiences with severe "rebound" phenomena following abrupt cessation of hormonal therapy together with the descriptions by Keeton and co-workers,[17] and Taran and Gulotta[18] who reported acute withdrawal symptoms in 25 of 41 patients, emphasize the importance of a slow, stepwise decrease in cortisone dosage when discontinuance of therapy is contemplated. In current studies, not presented in this paper, the impression has been gained that alternate courses of cortisone and corticotropin may be clinically more effective than repeated courses of the same hormone and may lessen the likelihood, possibly, of a serious "rebound."

There have been several instances of severe anaphylactoid reactions with ACTH.[5] Wilson[19] reported two cases of circulatory collapse during intravenous ACTH therapy. Subsequent skin testing disclosed no evidence of cutaneous sensitivity to ACTH. Three patients in our series developed a shocklike picture following the intramuscular injection of ACTH. Two of these patients appeared to have been aided by intravenous Benadryl. Thorn and associates[20] report that this type of reaction has become rare when highly purified corticotropin is employed.

The deleterious effect of ACTH or cortisone on the course of bacterial infections has been emphasized by other investigators.[14, 16, 21, 22] An acute exacerbation of sinobronchial infection was observed in 18 of the combined ACTH and cortisone-treated cases. Although these patients ultimately responded to appropriate antibiotic therapy, the persistence of an infectious process resulted in failure to obtain adequate relief from hormone treatment. The adverse reaction of cortisone on tuberculosis was strikingly apparent in the one patient who took cortisone over a 3-month period against advice and developed widespread bilateral involvement. Many chest films and sputum examinations in the preceding 5 years had been negative for pulmonary tuberculosis.

The significantly lower incidence of adverse reactions to hydrocortisone as compared with corticotropin and cortisone is probably related to the dosage of the steroid administered. Boland[23] observed fewer adverse effects with free hydrocortisone than with cortisone in the treatment of rheumatoid arthritis and attributed this difference to the smaller doses of hydrocortisone employed. This is substantiated by Thorn and co-workers,[24] who state that "the increased potency of hydrocortone without a proportionate increase in toxicity may be an important factor in making this steroid the hormone of choice in the therapy of diseases responding to corticotropin or the adrenal steroids."

At the initiation of our studies, it became apparent that weakness following the use of mercurial diuretics during administration of ACTH and cortisone could be ameliorated by the preparatory ingestion of potassium chloride. The advisability for potassium supplementation in all patients receiving these hormones has recently been emphasized.[25, 26]

The ideal indication for the use of ACTH, cortisone, or hydrocortisone in bronchial asthma appeared to be in patients with intractable bronchospasm due to seasonal allergens such as pollen. Because of the limited duration of these etiological factors, one or at most two short courses of hormone therapy will generally tide the patient over the period in which he is exposed to the exciting agent. The group of cases that responded next best in our experience were those in whom bronchospasm had been well-controlled by a bronchodilator regimen prior to the acute onset of severe asthma initiated by an upper respiratory infection. In contrast to these two groups, it was disappointing to note that the majority of patients with the chronic form of severe, intractable asthma had only short-lived remissions. Nevertheless, ACTH or the corticosteroids were extremely useful, perhaps even lifesaving, in many of those patients who were seriously ill since it allowed other bronchodilator measures to be employed subsequently under more favorable circumstances.

In patients with periarteritis nodosa, disseminated lupus erythematosus, and advanced pulmonary fibrosis with emphysema in whom the presence of persistent distention of the lungs would appear to shorten their life expectancy, maintenance therapy with ACTH, cortisone, or hydrocortisone seems justifiable. In chronic, severe, intractable asthma, maintenance programs have been resorted to when all other meansures have failed. From a practical standpoint, the aim has been to afford some relief of bronchospasm rather than a complete remission.

Despite the smaller dosage of ACTH or cortisone needed to accomplish this, varying degrees of hyperadrenalism inevitably result. Plotz, Knowlton, and Ragan[27] have pointed out that "the close parallelism of the spontaneous and induced forms of hyperadrenalism suggest potential hazards in long-term therapy with ACTH or cortisone." Since we have nothing better to offer this group, the authors feel that this calculated risk must be undertaken in the hope that the activity of the disease process might abate in time so that the physician might find it possible to treat the residual bronchospasm by other methods.

If further therapeutic trials substantiate our clinical experience that smaller doses of hydrocortisone, averaging 50 to 60 per cent of the cortisone level, are required for the control of severe bronchospasm accompanied by a marked decrease in the adverse reactions, then the risk of long-term therapy will be considerably reduced.

SUMMARY

A total of 163 patients with intractable asthma and pulmonary emphysema with bronchospasm were given 309 courses of ACTH, cortisone, or hydrocortisone. Complete or partial remission was observed in 82.3 per cent of the ACTH courses. Of the cortisone-treated patients, 86.2 per cent of the courses showed a similar response. Complete or partial relief of bronchospasm and dyspnea was observed in 96 per cent of the courses of hydrocortisone administered at a dosage level averaging 50 to 60 per cent of that employed with cortisone.

The duration of remission induced by the short, intensive courses of either ACTH, cortisone, or hydrocortisone was generally short-lived, averaging approximately 2 to 3 weeks. No significant difference in the duration of remission induced by these hormonal agents was found. Patients with bronchial asthma generally manifested a more complete remission than those with the bronchospastic type of pulmonary emphysema.

The effects produced with hydrocortisone differed from that of cortisone in the following manner: (1) a swifter onset of therapeutic benefit, i.e., in 18 to 36 hours with hydrocortisone as compared to 4 to 5 days with cortisone, (2) a decreased dosage requirement of approximately one-half to two-thirds of the cortisone dosage for comparable effect, and (3) a significant reduction in the adverse side reactions, due in all probability to the decreased dosage employed.

The best results from the use of hormonal therapy took place in the following two clinical entities: (1) patients in whom persistent bronchospasm was the result of exposure to seasonal factors such as pollen, and (2) patients in whom the asthmatic state had been previously moderately well-controlled but in whom intractable bronchospasm developed following an upper respiratory infection. Although short, intensive courses of ACTH or the steroids seemed preferable to maintenance therapy in these two groups, in 21 of the 30 patients with chronic intractable asthma, pulmonary fibrosis, and advanced pulmonary emphysema, clinical improvement was maintained for 9 to 24 months by a daily dose of 20 to 75 mg. of cortisone or hydrocortisone.

The adverse side effects of administration of the corticosteroids and ACTH were generally lessened by a low-sodium diet, administration of potassium chloride, and the use of antibiotic drugs in the presence of bronchial and sinus infections. The effectiveness of hydrocortisone at approximately one-half the dosage level of cortisone was accompanied by a significant reduction in the incidence of adverse side reactions. One patient who took cortisone against advice for 3 months developed bilateral pulmonary tuberculosis. One fatality occurred in a patient with severe bronchial asthma after repeated courses of both ACTH and cortisone. Delirium accompanied by exhaustion, fever, and cardiorespiratory failure suggested an Addisonian-like crisis.

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HISTOCHEMICAL STUDY OF THE MUCOPOLYSACCHARIDES IN LUNGS OF GUINEA PIGS SUBMITTED TO SHOCK BY DRUGS AND ANTIGENS

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IN RECENT papers on the histology of allergic reactions, Bohrod[1] and Firket[2] maintain that these offer no characteristic picture either in the cells or in the background elements, and that only the addition and combination of certain lesions provide an indication of their allergic nature.

Nevertheless, according to Miescher[3] it is to be expected that this lack of precision in these disorders would disappear altogether or partly, with the histochemical techniques used for nucleoproteins and mucopolysaccharides. Several of us have devoted clinical and experimental papers to the former[4-6] without attaining any well-defined results. On the other hand, the latter are acquiring an ever-increasing importance owing to the histochemical studies carried out on the normal[7-14] and pathologic[15-20] collagen, and on a few cells related to it.[21-27] Nowadays it is well known that there is a growing tendency to associate the diseases of the collagen to allergy,[28-31] but Klemperer's warning[32] that all disorders of the collagen are not necessarily of allergic origin, must not be forgotten.

This paper has been prepared for the foregoing reasons and with the purpose of carrying out a further study of the mucopolysaccharides in lungs of guinea pigs both normal and shocked by drugs and antigens. Our endeavor is to make the picture of experimental asthma more exact (in this case that of the animals shocked by antigens), because according to Ratner[33] the histologic changes due to their asthma are very similar to those in human beings.

MATERIAL AND METHODS

Thirty-two guinea pigs, divided into 3 groups, were studied. In the first, composed of 13 controls, 4 were given no treatment, being kept for comparison. The remaining 9 were submitted to various processes to find out whether during their preparation for experimental asthma, they developed any lung disorders which later might be attributed to it. For this purpose 2 were exposed to air pressure of 0.25 pounds per square inch in a glass bell, 2 were exposed to nebulized saline solution (pH 8.8) at the same pressure, 3 were exposed to nebulized 10 per cent albumin solution of the same pH for one, three, and six days, respectively. The remaining 2 were injected by the intraperitoneal route with 1 ml. of 10 per cent horse serum.

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In the second group of 4 guinea pigs, 2 were shocked 4 times by nebulizations of 0.5 mg. per cent acetylcholine on different days. The other 2 were similarly shocked with a 0.05 mg. per cent histamine solution. All were severely shocked.

In the third group of 15 guinea pigs, 9 were exposed for two hours on six successive days to nebulized 10 per cent albumin solution. After fifteen days they were given the same treatment for one week. The other 6 were given intraperitoneal 1 ml. injections of 10 per cent horse serum for one week. After fifteen days, they were exposed to the same solution nebulized for one hour on four consecutive days. All these animals showed a clinical picture of experimental asthma.

The 32 animals were killed by ether inhalation. More extensive details were published in a previous paper.[34-35]

For the histologic study of the lungs, a series of 8 micron sections were made; these were fixed in formaldehyde and Carnoy's solution, embedded in paraffin, and finally stained with hematoxylin-eosin, metanil yellow, May-Grünwald-Giemsa, and methyl green pyronine.

For the histochemical study of the mucopolysaccharides we used the following techniques: McManus and Cason (PAS)[36]; Hale's colloidal iron[37]; and the metachromic toluidine blue according to Lison's technique[38] with the variations recommended by Bachmann, Pedace, and Ruíz Moreno[39] (1 Gm. of toluidine blue in 800 ml. of distilled water; stain for 20 seconds). All these stainings were made directly and following the use of testicular hyaluronidase with 100 TRU per mg. prepared according to Tolksdorf, McCready, McCullagh, and Schwenk's method[40] and applied according to Bunting and White's procedure.[18] To distinguish part of the mucopolysaccharides studied, we used Mayer's nomenclature.[9]

RESULTS

All of the techniques gave positive results, both in the animals submitted to shock and in the controls, but with quantitative variations between the three groups.

In Table I the techniques are distributed according to their presence or positiveness. The controls are shown by a square (□); the animals shocked with drugs by a triangle (△), and a circle is used for the animals with experimental asthma (○). By these means it is possible to identify the positive reactions in the lumen contents, in the mucosa, the edema of both the bronchial wall and cartilage, and also in the cells of the lax peribronchial tissue.

Furthermore, the positive substances obtained in the lumen contents, in the fibrinoid alteration and in the edema situated between the arterial walls, are shown, and also those in the contents of the veins and capillaries. Finally we show the substances found in the alveolar lumen and in the cells with Kurloff bodies which appear disseminated in the pulmonary parenchyma.

We now consider the positive reactions in each of the three groups separately.

First Group. Controls.—In the contents of the lumen and the cells of the bronchial mucosa, toluidine blue gave positive metachromasia, and PAS a positive reaction (Fig. 1) which disappeared after an application of hyaluronidase (Fig. 2), thereby proving the presence of mucoitin-sulfuric acid. On the other hand, these same reactions appeared in the cartilage, but disappeared when hyaluronidase was applied previously (Figs. 1 and 2). In the mastocytes only positive metachromasia was found (Fig. 3). This also was abolished by hyaluronidase.

TABLE I

Techniques	BRONCHI					BLOOD VESSELS					LUNG PARENCHYMA	
						Arteries			Veins			
	Lumen Contents	Mucosa	Peri-bronchial Edema	Cartilage	Mastocytes of the Lax Peri-bronchial Tissue	Lumen Contents	Fibrinoid Change	Edema of the Walls	Lumen Contents	Capil-laries	Alveolar Lumen Contents	Cells With Kurloff's Corpuscles
Toluidine Blue	○ △ □	○ △ □	○ △ □	○ △ □	○ □			○			○	
Hyalu-ronidase Toluidine Blue	○ △ □	○ △ □										
PAS	○ △ □	○ △ □	○ △ □	○ △ □		○ △ □	○ △ □	○	○ △ □	○ △ □	○	○ △ □
Hyalu-ronidase PAS	○ △ □	○ △ □				○ △ □	○ △ □		○ △ □	○ △ □		○ △ □
Colloidal Iron	○ △ □	○ △ □		○ △ □								
Hyalu-ronidase Colloidal Iron	○ △ □	○ △ □		○ △ □								

○ = Guinea pigs shocked with antigens (experimental asthma)
△ = Shocked with drugs
□ = Controls

From the foregoing we gather that chondroitin sulfate A is found exclusively in the cartilage. Heparin, another mucopolysaccharide acid (probably related to mucoitin-sulfuric C acid found in various connective tissues) was found in the mastocytes.

A fine positive red metachromic network (which also gave positive reactions with PAS that disappeared after hyaluronidase) appeared in the edema situated between the mucosa and the bronchial cartilage of a small number of bronchi in the animals under air pressure, in the 2 nebulized with the saline solution, and the 2 nebulized with albumin. From these results we presume that the substance contained mucoitin-sulfuric C acid.

The colloidal iron reaction gave positive results (blue) in the lumen contents, in cells of the mucosa and bronchial cartilage, in the nuclei of the internal

and middle tunicae of the lung arteries, and in the nuclei of the cells in the lung parenchyma. After the use of hyaluronidase, the reaction was equally positive, there being no variations of any kind. The only point worth mentioning is that the mucosa of the bronchioles—which seldom reacts positively to other stains—always appeared blue after colloidal iron reaction (Fig. 4).

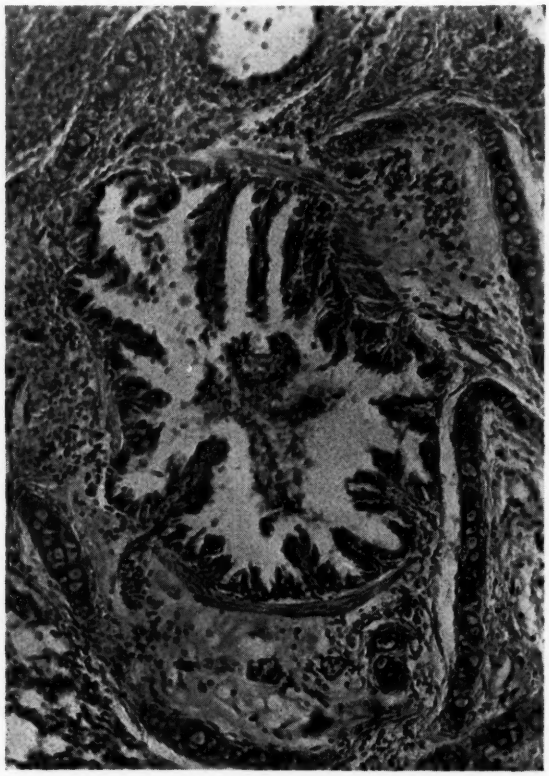

Fig. 1.—Control nebulized with 10 per cent albumin one day for two hours. Topographic view of the bronchial wall in which the cartilage mucosa and lumen contents are shown up with positive metachromasia (toluidine blue).

Furthermore, a PAS positive reaction was obtained in the plasma contents of the pulmonary vessels, which was not abolished by previous hydrolysis with hyaluronidase. This reaction was also found in the walls of some arterioles in the animals submitted to air pressure, in 2 of the animals nebulized with albumin, and in one of those injected with serum. The aspect presented by this reaction was one of fibrinoid alteration. These PAS positive substances, resistant to the action of hyaluronidase and which did not give positive metachromasia, must be a compound of nonacid mucopolysaccharides which react only to PAS.

Finally in the cells with Kurloff bodies disseminated in the lung parenchyma of all the controls, a PAS positive substance appeared which had the same properties as those described previously.

Second Group Guinea Pigs Shocked With Drugs.—The reactions obtained in this group of animals were similar to those in the controls (see chart).

Third Group. Guinea Pigs With Experimental Asthma.—The reactions in the lumen contents in the mucosa (Fig. 5), in the bronchial cartilage, as also those in the plasma of the blood vessels and in the fibrinoid alteration in the walls of the latter (Fig. 6), in the mastocyte granulations and in the Kurloff bodies (Fig. 7), were the same as those obtained in the 2 previous groups (see Table I).

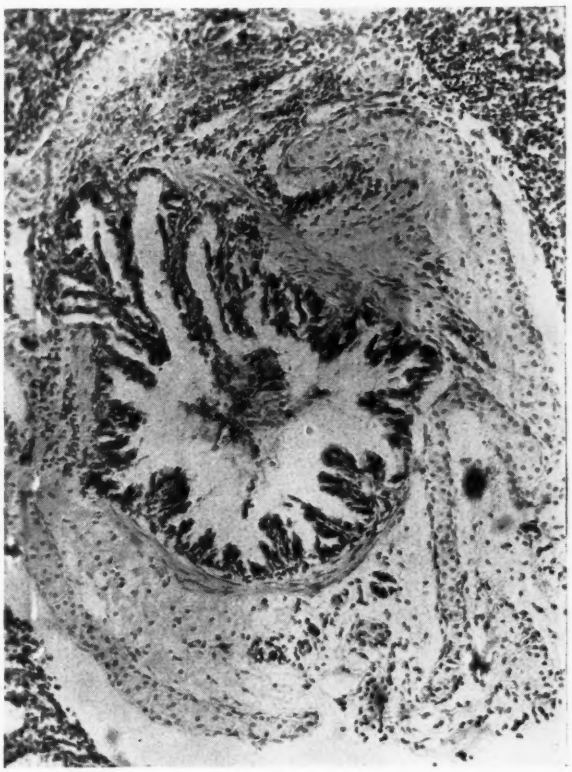

Fig. 2.—The previously mentioned bronchii (Fig. 1) after application of hyaluronidase. Note that positive metachromasia disappeared only in the cartilage. (toluidine blue).

On the other hand, in 13 of the 15 guinea pigs, a moderate amount of edema appeared situated between the mucosa and the cartilage of the bronchi (Fig. 8). In this edema we found a fibrillar substance which gave positive metachromasia and positive PAS reaction (abolished by previous application of hyaluronidase). In this group this substance appeared in more bronchi and in greater quantity than in the 2 groups already mentioned. However, as it had the same properties as that in these first groups, it must be the same substance, i.e., mucoitin sulfate C.

On the other hand, a substance, not seen in the first 2 groups, appeared in the edema of the walls of some arterioles in almost all the animals shocked with horse serum. Its appearance was fibrillar and gave a positive metachromasia

and was PAS positive. The reactions did not appear when hydrolysis with hyaluronidase took place. We suppose, therefore, that this substance is similar to the chondroitin sulfate C found in the edema of the bronchial walls.

A substance, metachromic when stained with toluidine blue (Fig. 9), that turned violet, not red, and which also was PAS positive, was found in the lumen of many alveoli in only 2 of the animals most intensely shocked with horse serum. These reactions were partly cancelled by previous treatment with hyaluronidase. This substance could be the chondroitin sulfate C mentioned previously, although it is slightly different. For a more exact definition of its nature, further studies are necessary.

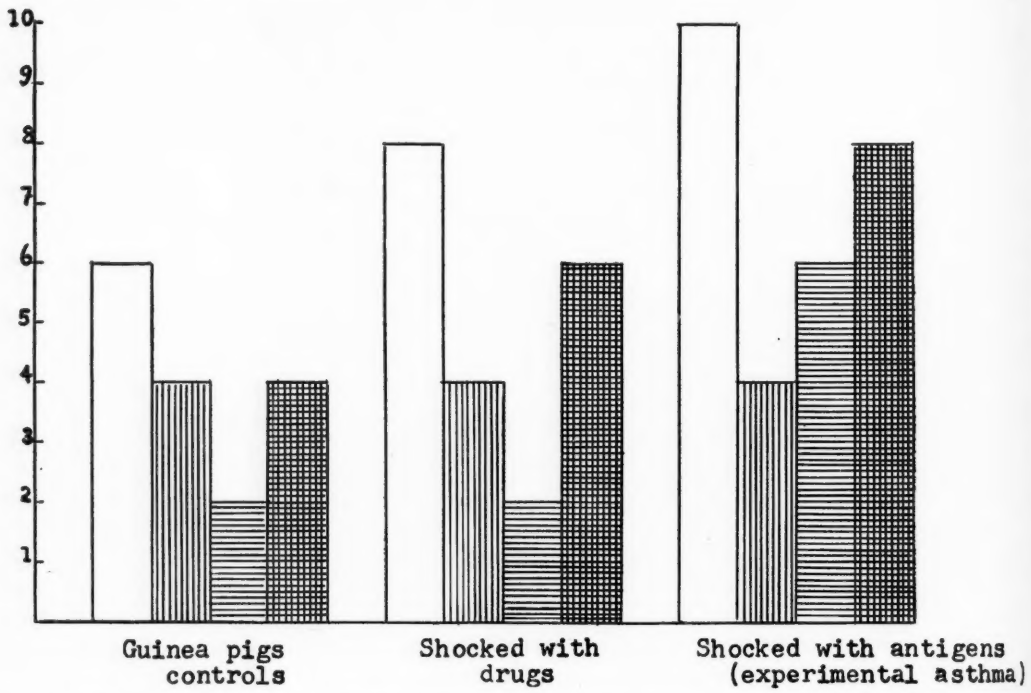

Chart I.—White column: Mucoitin sulfate acid. Vertical lines: Chondroitin sulfate acid A. Horizontal lines: Chondroitin sulfate C acid. Squares: Nonacid mucopolysaccharides.

In Chart I, the mucopolysaccharides found in the 3 groups are distributed according to a conventional valuation of 1 to 10 to the quantity of each one in each group of guinea pigs. In the white column the mucoitin-sulfuric acid is shown; chondroitin sulfate A is shown in the column with vertical lines; chondroitin sulfate C in that with horizontal lines and nonacid mucopolysaccharides in the column of squares.

It can be seen how the mucoitin-sulfuric acid increased in the animals shocked with drugs and, above all, in guinea pigs with experimental asthma. This is due to the greater output of mucus seen in these animals both in the contents of the cells of the bronchial mucosa as well as in the large number of mucosal plugs which blocked the lumen.

On the other hand, chondroitin sulfate A appeared unchanged in the 3 groups, as the cartilage did not seem to be modified to any great extent.

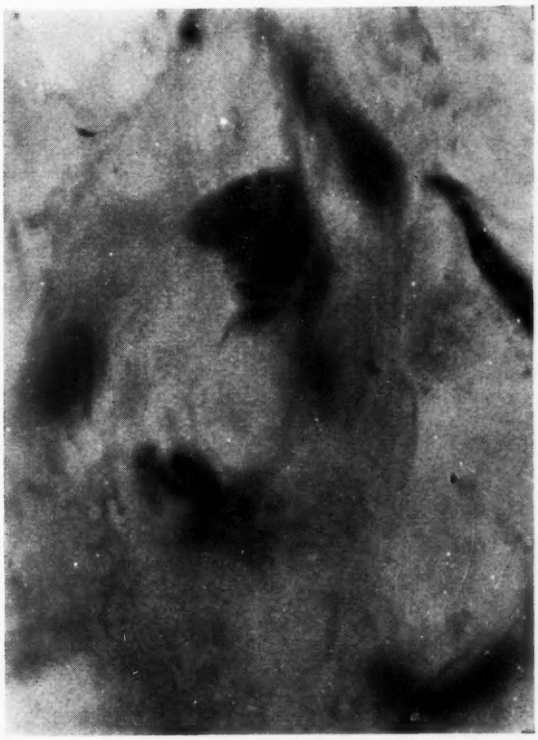

Fig. 3.—Mastocyte in the lax peribronchial tissue of an animal (control) injected with horse serum 1 ml. showing the positive metachromic granulations (toluidine blue).

Above all, chondroitin sulfate C increased in the guinea pigs with experimental asthma because they had a larger number of bronchi with a greater quantity of edema than the other animals. Also, only in these was there any edema between the arterial walls and effusion in the alveoli, conditions which apparently were caused by the said acid.

The nonacid mucopolysaccharides in the arterioles with fibrinoid disorders, and in the cells with Kurloff bodies, notably increased in the animals with experimental asthma. This was due to the presence of a larger number of arterioles with fibrinoid changes and the increased amount of cells with Kurloff bodies found in these animals.

COMMENTS

In this paper, the only metachromic reaction considered is that obtained by using one basic stain derived from Thyacine (Lison[38]). This metachromic reaction, according to Lison and Matsaars'[41] most recent denotation is called positive metachromasia. Therefore, other reactions, which although they are

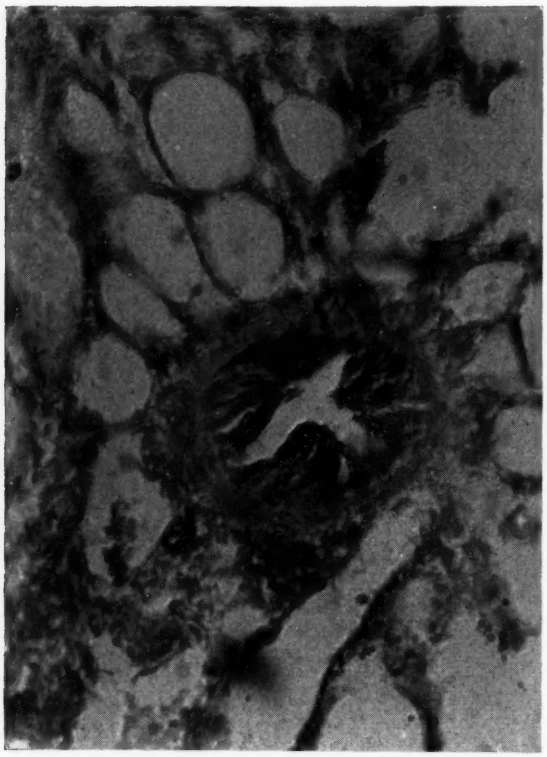

Fig. 4.—A small bronchial of a control injected with 1 ml. of horse serum showing the intense positive Hale reaction in the mucosal cells and in the nuclei of the lung parenchyma.

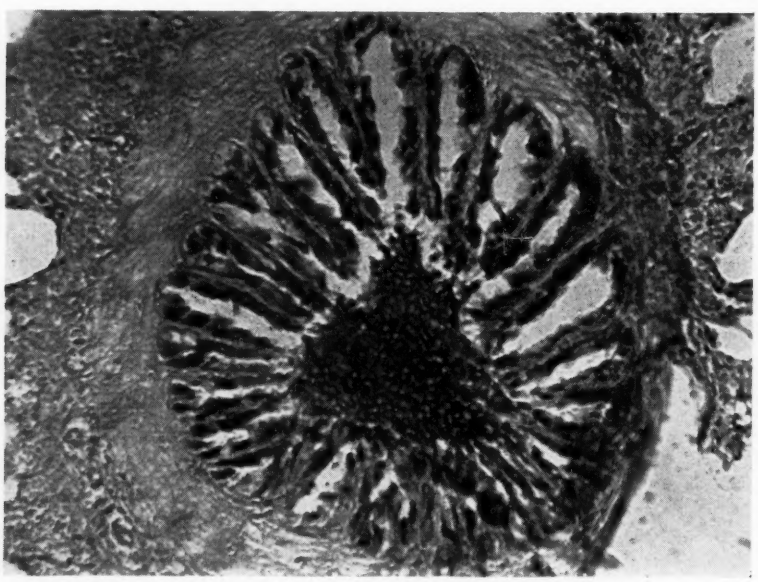

Fig. 5.—A medium-sized bronchial of an animal with experimental asthma through nebulizations of horse serum. Note the intense red stain (PAS) of the mucosal cells and the lumen contents.

Fig. 6.—Fibrinoid change and edema of the wall in an intensely red arteriole from an animal with experimental asthma through nebulizations of 10 per cent albumin (PAS).

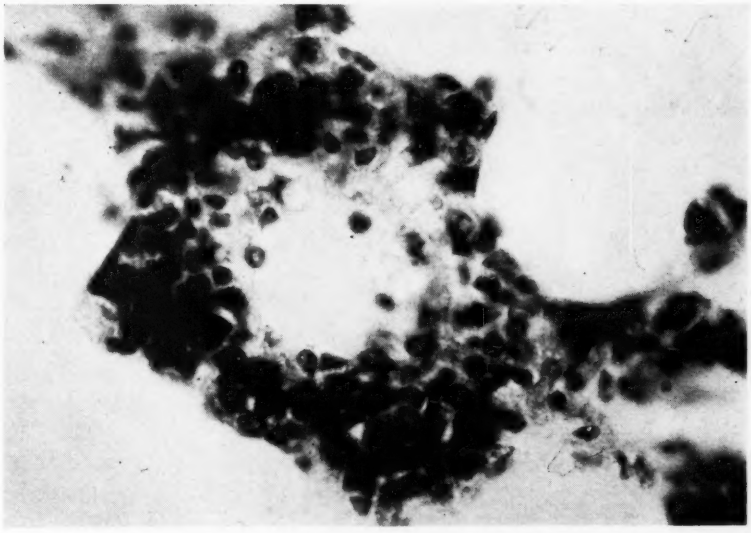

Fig. 7.—Intensely red cells with Kurloff bodies in the lung filtrate of an animal with experimental asthma through nebulizations of 10 per cent albumin (PAS).

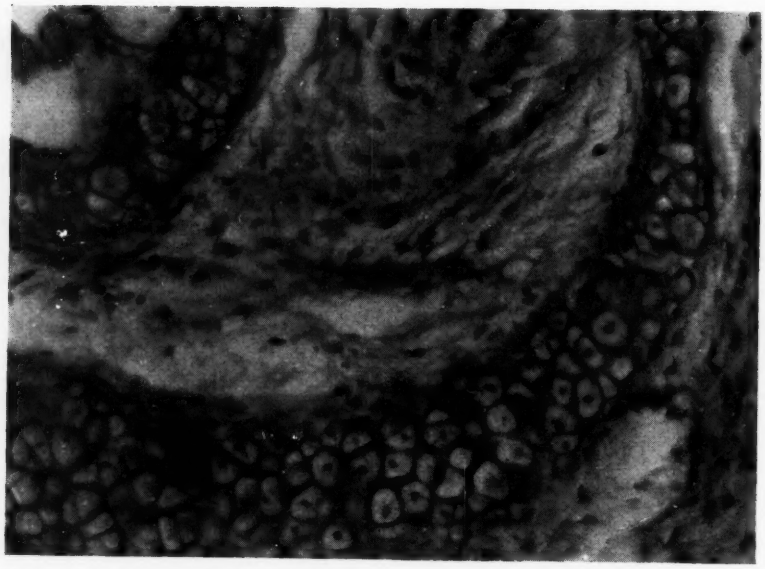

Fig. 8.—Animal with intense experimental asthma through nebulization with 10 per cent horse serum. View (slightly enlarged) of the edema situated between the wall of the cartilage and mucosa where a filmy net with positive metachromasia (toluidine blue) can be seen.

Fig. 9.—Exudate in the intensely red alveolar lumen of an animal with experimental asthma through nebulizations of 10 per cent horse serum (PAS).

metachromic in so far as their color is different to that of the original stain used, are excluded from this denotation because they do not fulfill the aforesaid conditions, for instance, PAS, which some define as metachromic.[16]

Nevertheless, owing to the large concentration of toluidine blue used in our experiments (1:800) the objection could be raised that the metachromic reaction obtained was not a true one, because Lison[38] and Hempelmann[42] maintain that true metachromasia is obtained only when small concentrations are used (i.e., 1:1,250,000). It must be borne in mind, however, that not only the concentration of the stain, but also the exposure time acts upon the tissues. In fact, the authors mentioned allow the stain to react for ten hours, whereas we expose it for only twenty seconds.

We conclude, therefore, that the final results are practically the same, as the mathematical relation in the exposure time is inversely proportional to the concentration of the coloring.

The positive results obtained with the colloidal iron reaction in specimens fixed in Carnoy's solution—a fluid which preserves hyaluronic acid—cannot be attributed to this acid. Actually the positive blue reaction was obtained in the lumen contents, in the cells of the mucosa, and in the bronchial cartilage. This was also observed by Lillie and Mowry[43] and by Ritter and Oleson.[17] Again the reaction was positive in the nuclei of the endothelium and walls of the blood vessels—already described by the authors mentioned previously—and also in the cell nuclei of the lung parenchyma. McManus, Lipton, and Graham[10] obtained similar results in nuclei of the renal cells. For the previously stated reasons and because the positive reaction did not disappear with previous treatment with hyaluronidase, we infer that Hale's colloidal iron reaction is not specific to hyaluronic acid, because, although the reaction to this acid was positive, the same result can be obtained with other substances.[10-11, 43-44]

Perhaps in future studies dedicated to this acid alone, it would be preferable to use frozen specimens, as recommended by Firket[2] and by Holt, Sommers, and Warren.[45]

The positive PAS reaction in the fibrinoid alteration of the vessels of the guinea pigs with experimental asthma, coincides with descriptions by other authors.[5, 7, 16, 36] However, this same reaction appeared in a smaller degree in the vessels of the control animals exposed to nebulized albumin and in the animals injected with horse serum, and also in one of those shocked with histamine.

This indicates that the experimental vascular fibrinoid change, which Zeek[46] has recently defined as "hypersensitivity angiitis," is not pathognomonic of the experimental allergic reactions as maintained by Klinge,[47] Vaubel,[48] Rich and Gregory[49] and many others, but appears also in other phenomena which are not necessarily allergic.[1-2, 31-32]

That is why it was found in the vessels of animals with experimental streptococcal infection,[50] with histaminic shock,[28, 51] orthostatic collapse,[52] in the periods of resistance and exhaustion in adaptation syndrome,[28, 53] and even in the vessels of apparently normal rats.[54]

On studying the positive reactions of PAS and toluidine blue in the mucosa, the lumen contents and in the bronchial cartilage, the positive results already commented on and described by many authors were found.[7-11]

On the other hand, in the edematous zones of the bronchial walls and arterioles, in the effusion which blocked the lumen of some alveoli, we found a substance which, as it gave positive metachromasia and was PAS positive (positiveness cancelled after hydrolysis with testicular hyaluronidase) according to Mayer and Rapport's classification,[13] can be considered for the present as chondroitin sulfate C. These authors found this substance in the valves of the heart, the aorta, the tendons, and the umbilical cord, and it is one of the mucopolysaccharides of the background material forming the connective tissue[6] and, according to Miale[55] is not yet sufficiently known. It is possible that in those zones which also have connectivum, the substance described as chondroitin sulfate C manifests itself, thanks to the edema which makes it show up. This substance is not similar to hyaluronic acid as it has been found in specimens fixed in Formol and it is a well-known fact that hyaluronic acid is soluble in this solution and therefore does not appear (Hale[11, 37]).

Chondroitin sulfate C was found only in the edema of the alveolar walls and of the lumen in some of the alveoli in the animals with experimental asthma. On the other hand, it appeared in the edema of the bronchial walls of these animals, in the controls and those animals shocked with histamine, although in a smaller number of animals and fewer bronchi (5 of the 13 controls and 1 of the 4 animals shocked with drugs).

It is unusual for bronchial edema to appear in an animal shocked with histamine, and Halpern[56] found it only in the bronchi of animals shocked with antigens. The explanation for its appearance in our experiment could be that histamine alters the vascular permeability, thereby encouraging the formation of edema (Da Rocha e Silva[57]).

It is more difficult to explain the edema which appeared in the bronchi of the 2 guinea pigs submitted to air pressure, in one of those nebulized with pH 8.8, and in the two nebulized with 10 per cent albumin solution and pH 8.8. All these animals were controls. This edema could have been due to the inflammatory action of the nebulizations with the alkaline pH or to some respiratory infection which is so prevalent in laboratory rodents (Lauche[58] and Seifried[59]).

From all these experiments we conclude that although the histochemical study of mucopolysaccharides can give a deeper insight into certain processes which occur in the evolution of allergic inflammation in experimental asthma, it does not, at least for the present, give an exclusive definition of the picture, because all the mucopolysaccharides we found in this type of asthma appeared (though in a smaller amount) in the guinea pigs shocked with drugs and also in the controls.[7]

At present, only the quantity of the mucopolysaccharides together with their group formation can allow us to suppose that a picture of experimental asthma exists. This statement is corroborated by Bohrod[1] and Firket.[2]

CONCLUSIONS

1. The application of histochemical techniques in the study of lungs in guinea pigs, revealed the presence of various polysaccharides both in the controls and in the animals submitted to shock with drugs and antigens.

2. It was proved that in the edematous areas and the contents of the alveolar lumen in animals intensely shocked by antigens, a substance was present which, owing to its metachromic properties (that were destroyed by previous administration of hyaluronidase), can be assumed to be an acid mucopolysaccharide possibly containing sulfur, of the type of chondroitin sulfate C.

3. The fibrinoid change, which is observed in the blood vessels of the animals shocked by antigens, is not typical of experimental vascular allergic phenomena, as it was also seen in the vessels of guinea pigs shocked with histamine, and even in the vessels of the apparently normal controls.

4. For the present at least, a mucopolysaccharide does not exist which, merely by its presence in the lungs of guinea pigs shocked by antigens, allows us to state categorically that it is due exclusively to an allergic process.

SUMMARY

By means of histochemical techniques using toluidine blue, coloidal iron, and PAS, and with the pre- and postexperimental application of hyaluronidase, a study was made of the mucopolysaccharides in the lungs of normal guinea pigs and of guinea pigs shocked with drugs and antigens. Although mucopolysaccharides of the chondroitin sulfate C type appeared in the lungs of the guinea pigs intensely shocked by antigens, it cannot be stated with certainty that these are exclusive to experimental allergic phenomena.

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STUDIES IN SENSITIZATION AS APPLIED TO SKIN TEST REACTIONS

I. Do Skin Test Reactions Change?

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DESPITE certain drawbacks and disadvantages, allergy skin tests still are the most important and most widely used method of diagnosis employed in allergic diseases. While differences in application or in technique exist, nevertheless most allergy patients seen by either the practicing physician or the allergy specialist have some form of skin tests performed upon them as part of the diagnostic study. Following the performance of such tests, the resultant reactions are recorded and reported. Whenever possible, attempts also are made to determine whether the positive reactions are of clinical significance (a *clinical positive*) either by correlation with the patient's clinical history or by some form of clinical trial. Despite differences of opinion expressed by many authors as to the need or desirability of doing skin tests, especially in patients with clinical manifestations of food allergy, skin-testing methods nevertheless can be and often are of considerable aid in the management of allergy patients and are widely utilized for that purpose.

During the course of daily allergy practice the question sometimes is raised as to whether skin test reactions change either spontaneously or perhaps as the result either of abstinence or of treatment. Thus, for example, we sometimes are asked by patients who have eliminated positive-reacting foods for varying periods if they can be retested to determine whether or not these foods can be added again to the diet safely. They have the idea, often shared in or even suggested by the attending allergist, that improvement in their tolerance for that food should be demonstrated or accompanied by a decrease in the size of the skin reaction and therefore that retests can be utilized as a means of detecting the improved tolerance.

This question also comes up when patients return to the attending allergist, after a lapse of some years, because of a recurrence of symptoms. Many such patients are retested, not only to determine or to detect new allergies which may have arisen in the interval, but also to see whether there has been any change in their sensitivity during the elapsed interval as indicated by their skin test reactions.

Then finally, in patients receiving specific desensitization treatment, particularly for pollen hay fever, the question often arises as to whether they should be retested to determine if they are showing improvement and whether treatment can be discontinued. In fact it has been (and perhaps still is) the practice of some allergists to retest patients at the conclusion of the pollen season with this thought in mind.

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These are pertinent questions which often present themselves to the practicing allergist and to which we have no definite or certain answer. In fact, we ourselves have been puzzled about them for a long time and have never been sure that the advice we gave was correct, since it was based purely upon clinical experience rather than upon accurately obtained data. Because of our uncertainty and perhaps as the easiest way out, we usually retested such patients, either when the patient requested it or when we felt that it was justified either to detect newly acquired sensitivities, as in patients returning after a reasonably long interval, or in those in whom we wanted to determine the effect either of complete abstinence or of specific treatment (as in patients with food allergy or hay fever).

Actually we are not on very firm ground in our answers to these questions. For example, there is little basis for stating, except from our own clinical experience, that positive skin test reactions will decrease or increase according to the extent of the patient's subsequent exposure to the offending allergen or as the result of any treatment which we have instituted, either specific or otherwise. Under those circumstances, any advice to such patients necessarily must be uncertain, problematical, and given "with tongue in cheek." Because of this uncertainty and confusion it was thought that a clinical study of this problem might shed some light upon these questions and perhaps even supply more satisfactory answers. The data obtained in our investigations on whether skin test reactions change form the basis of the present report.

In attempting to review the literature on this subject we found few helpful references. Thus, for example, most of the textbooks or monographs on allergy contain little about possible changes in skin test reactions, except in relation to treatment. Some of the older textbooks and literature contained references to discussions and papers presented at annual conventions as to whether skin test reactions were affected by pollen desensitization. While there was no consensus concerning this problem, most allergists seemed to feel that there was little change in the skin test reactions after pollen therapy and that this method probably should not be utilized to determine if the patient had acquired an increased tolerance to the pollen as a result of the treatment. Actually this still is determined either entirely by the clinical course of the patient during the hay fever season or perhaps by the use of such clinical tests as the quantitative pollen nasal tolerance test.[1]

In discussion of the interpretation of the positive skin test reactions particularly in relation to the nonclinical positive representing past sensitivities, it often is pointed out that skin test reactions are likely to persist long after the initial sensitization and after it has lost its clinical significance. Upon that basis one would not anticipate much change in the skin test reaction over a period of years even despite the avoidance of such offending allergens as foods. Yet Peshkin[2] recently stated that upon the basis of previous studies, avoidance of the test-positive food was followed after an interval (extent not stated) by reduction in the degree of the skin test reaction often to negative

(these tests were done by the scratch method). Also, in a personal discussion with Kremer of Amsterdam, Holland, I was told that he (and possibly other European allergists), when treating patients with food allergy, would have them eliminate a test-positive food from the diet until they were symptom-free. He then would retest the patient to that food intracutaneously and, if the reaction was negative, he would again add it to the diet. This experience is verified in an article published recently by Kremer[3] in which he cites several patients in whom after avoidance of foods for varying periods, intracutaneous skin tests were negative and upon this basis the food was again added to the diet. One not infrequently finds similar opinions and practices in reading publications devoted to other subjects—for example, in Nexmand's monograph on "Besnier's Prurigo"[4] he cites a patient with atopic dermatitis who gave a positive skin reaction to horse dander. This became negative a month after desensitization with horse dander extract was instituted but returned twenty-one months later after treatment was stopped and symptoms had recurred. By contrast, the positive reaction to cat dander remained unchanged. Aside from this, however, we found little in the old or current literature relating to the question of retests.

Since our review revealed such a striking difference of opinion, we felt that before proceeding with our own investigation, it might be well to find out what was the current practice and opinion of allergists regarding positive skin test reactions and the possibility of their changing. Accordingly, questionnaires asking for this information were sent to all fellows and most of the members of the American Academy of Allergy. It first was our intention to send them to fellows only, since they were sent merely for our own edification. Answers to these questionnaires proved so interesting, however, that we decided to send the balance of our supply to as many members as possible in order to get their reaction as well. The data thus obtained were quite revealing, and with the thought that the results might be of interest to those answering the questionnaires as well as to other readers, we thought it worth while to report it in more detail than originally intended. While most of the information obtained related to the subject of retests, in which we were primarily interested, there also was included considerable information and unsolicited comment, which reflected the opinion and attitude of allergists toward our present skin testing methods and their interest in our attempts to clarify this subject.

QUESTIONNAIRE DATA

Of the total of 350 questionnaires mailed out, responses were obtained from 310. This is indeed a gratifying proportion and indicates the intense interest which the recipients had in this subject. In fact, many who answered the questionnaire amplified their comments by additional letters expressing detailed opinions and were quite willing to have their names used, even though it was made clear that their identity need not be known.

The questions asked of the members were listed in five general categories. These are listed in Table I which also contains a summary of the answers obtained. Inspection of this data reveals, in the first place, that although most

allergists believe that skin test reactions lessen in degree, they differ as to whether this is the result of food avoidance. While there were more affirmative answers than negative, this cannot be considered the predominant opinion, since many doubted its occurrence or felt that it was rare. Furthermore, about one-third left the space blank presumably because they were uncertain of the answer. One can only conclude from this that while some allergists believe that skin test reactions lessen after food avoidance, theirs is a minority opinion. By contrast, the majority of allergists who replied to this question felt that specific treatment brings about or is followed by reduction in the skin test reaction.

TABLE I. SUMMARY OF DATA OBTAINED FROM REVIEW OF 310 QUESTIONNAIRES

QUESTION ASKED	YES		NO		DOUBTFUL OR RARE		NO ANSWER	
	NO.	%	NO.	%	NO.	%	NO.	%
In your opinion do positive skin tests lessen in degree?	270	87	25	8.1	8	2.6	7	2.3
Was this the result of:								
(a) Avoidance (as with foods)	97	31.3	53	17.1	52	16.8	108	34.8
(b) Specific or other treatment (desensitization)	186	60	26	8.4	38	12.2	60	19.4
(c) Miscellaneous reasons	231							
Do positive skin tests ever become negative in your experience?	160	51.6	64	20.6	22	7.2	64	20.6
Do you retest patients?	305	98.4	5	1.6				
Reasons								
(a) Treatment ineffective	127	43.9						
(b) New symptoms	65	22.5						
(c) All pollen cases	70	24.3						
(d) Miscellaneous	27*							
Retest to see if foods can be eaten again?	93	30	213	68.7			4	1.3
Advice of allergist	198	63.9						
Request of patient	4	1.3						
Both (advice and request)	82	26.4					26	8.4
Interval between tests	6 weeks to 15 years; average period 3 months to 5 years							

*Per cent could not be listed because of duplication.

When asked whether there were other reasons for the reduction, a great many miscellaneous causes (listed in Table II) were mentioned, but without substantiating evidence to support the contention that such factors are or could be responsible for the alteration.

While the question, "Do skin tests ever become negative in your experience and under what circumstances?" seemed a duplication of an earlier question asking, "In your opinion do positive skin tests lessen in degree?" we included it originally in order to find out whether allergists thought a positive skin test reaction ever became completely negative regardless of its degree. Apparently some felt that this could happen, for reasons which varied from specific treatment or desensitization to avoidance or advancing age. This was of particular interest to us because of its relationship to the problem about which we were seeking information and which had prompted the present investigations.

Question 2 was asked as follows: "Do you retest patients at any time; if no, why not and if yes, under what circumstances and after how long an interval?" The "Yes" response to this question was practically unanimous

Only five of the entire group answered in the negative. The reasons given were because he "did not retest foods," or thought "it did not indicate the degree of sensitiveness," or "was not worth the time, money or information gained," or because he was "guided simply by the history and symptoms of the patient," and finally "because of the variability of the testing material." With these rare exceptions, however, most allergists apparently have occasion to retest their patients.

The replies to the question asking about the circumstances prompting the retests indicated that allergists frequently retest their patients, either because of unsatisfactory treatment results or because of the appearance of new symptoms which could not be explained by their previous tests. As shown in Table I, the interval between the original testing and the retesting varied considerably depending upon the particular indication.

TABLE II. QUESTIONNAIRE DATA—REASONS GIVEN FOR DECREASED SKIN REACTION OR FOR ITS BECOMING NEGATIVE

Pathologic		*Physiologic*	
19	specific disease or other illnesses	31	age
3	acute or chronic infection	26	spontaneous (idiopathic)
2	after acute asthma	4	puberty
Technical		2	menopause
16	variability of test solution	2	pregnancy
4	variance or inaccuracy	2	endocrine
3	areas of skin used	2	fatigue
		1	biochemical change
		1	improved health
		1	change in season
Therapeutic			
53	pollen therapy or treatment		
6	antihistaminics before tests		
5	use of drugs (including ACTH or cortisone)		
Immunologic			
26	avoidance of allergen		
9	altered sensitivity or shock organ (changes in reagin titer or less histamine in skin)		
8	foods only become negative		
2	nonatopic (horse serum, insulin, penicillin)		
2	amount of allergen in environment at time of test		
1	anaphylactic shock		

We were especially interested in the response to the question which asked if the retests were done upon the advice of the physician or because the patient requested it. This was put in because patients often ask the allergist about the advisability of being retested with positive-reacting foods and the physician in turn does so either because he himself is not sure or as the path of least resistance. We got the impression from review of the responses that retests were suggested by the allergist first in patients with hay fever requiring pollen retests, whereas in those in whom it was a question of food retests the suggestion first was made either by the allergist or by the patient or perhaps by both. Thus 26.4 per cent answered that it was at the advice of both allergist and patient, which tends to verify the latter statement.

The answers to the question asking, "In patients eliminating foods giving positive skin reactions do you retest the positive reactors to see if the food

can be eaten again?" were of particular interest to us in relation to our own investigations. The replies indicated that many allergists use skin tests as a criterion for the readdition to the diet of test-positive foods which the patient had been avoiding and that the interval varied between one month and three to four years.

Included in the questionnaire was a question inquiring about the technique of testing used. While this was not directly related to the problem with which the questionnaire was concerned, it was included in order to find out more definitely what technique is used by most practicing allergists, about which most of us have only at best a vague impression. As seen in Table III a majority of allergists (58.7 per cent) use a combination of the scratch and intracutaneous methods. A lesser proportion (36.4 per cent) use the intracutaneous alone, whereas comparatively few use either the scratch test alone (2.3 per cent) or the puncture-prick test combined with the intracutaneous (2.6 per cent). Where the scratch and intracutaneous methods were used, the statement usually was made that the scratch test was used first, and that all negatives were retested by the intracutaneous method. In a few instances it was stated that the scratch method was used only where a definite clinical history of severe reaction was obtained, but otherwise patients were tested by the intracutaneous method. One responder, apparently in defense of the intracutaneous method, stated that he "used the scratch test only for 13 years and then gradually switched to the intracutaneous with much better results." In contrast, another blamed the intracutaneous method for "too many false positives."

TABLE III. QUESTIONNAIRE DATA AS TO TESTING METHODS

TESTING METHOD USED	NO.	PER CENT
Intracutaneous	113	36.4
Scratch	7	2.3
Intracutaneous and scratch	182	58.7
Puncture (or prick) and intracutaneous	8	2.6

The final question which was included in the questionnaire was labeled "Special Comment." This elicited considerable information and provocative comment, which further emphasized the natural interest which allergists have in the subject of skin testing. Many responders expressed the necessity for improvement both in our testing methods and more particularly in methods of standardization. Likewise, many commented upon the variability in the testing material and the need for properly standardized, potent, and reliable extracts. Some criticism was directed against the technical inaccuracy of tests done, especially by untrained or improperly trained workers using irritating extracts or injecting too large amounts (0.05 or 0.1 ml.) when doing intracutaneous tests.

Much of the special comment concerning skin tests pertained to the old and often discussed question of the reliability or unreliability of tests done with food extracts and the question of interpretation. For example, about

one-fourth of the responders frankly expressed the viewpoint that food tests either were valueless or were of such doubtful value as to be entirely unreliable or "misleading." Usually those who expressed such comment stated that they relied either entirely upon the history for determination of the sensitivity to foods, or more frequently upon elimination or trial diets. Even those who initially skin tested with food extracts stated that they preferred diet trial to skin tests in determining whether a test-positive food can be added to the diet again. There were several emphatic comments about the desirability of doing skin tests with more potent extracts of foods or about the need for improvement of the materials with which food tests were done. By contrast, it was stated by others that "food tests help to eliminate positives in diet trials," and also that "the average allergist is woefully weak in recognizing and handling food allergies properly."

Not all the comment was completely unfavorable. Many allergists expressed the opinion that skin testing was an important part of the allergist's diagnostic armamentarium, that they should be utilized as aids in diagnosis just like the electrocardiogram or the x-ray, and that skin test results could be very helpful if they were interpreted according to facts elicited by a carefully taken clinical history.

Surprisingly little comment was made in answer to the question of skin testing methods as to which technique was preferable. The old debate about scratch versus intracutaneous technique received little consideration chiefly because few employed scratch tests alone. Those who did both types of tests frequently used the intracutaneous method for negative reactors or used the scratch test as a means of preventing possible constitutional reactions in patients giving a clinical history of marked sensitivity (e.g., to fish, egg, etc.). Actually, little mention was made about the dangers of constitutional reactions; in fact, some voiced the opinion that with present-day care in the dilutions of extracts and in testing methods, constitutional reactions to skin tests have become extremely uncommon.

Many responders definitely opposed the performance of large numbers of tests without reason or merely as a routine. One gets the impression from this review that there is a great need for the streamlining of our testing methods in order to shorten the procedure while at the same time making it easier for practitioners other than allergists to know which skin tests are considered worth while doing; also for proper standardization of our extracts so that all may be using uniform materials and tests.

PERSONAL STUDIES

According to the information obtained in the questionnaires, most allergists believe that skin test reactions lessen in degree and may even become negative, also that alteration can follow prolonged specific desensitization (mostly pollen). However, opinion is divided as to the possible influence of food avoidance. Less than one-third of the responders retested their patients to determine whether a positive-reacting food could be again added to the diet.

Theoretically according to present knowledge and clinical experience, what are the possibilities? First, new positives obviously must arise with continued exposure. This certainly is verified by clinical experience, for infants and young children acquire sensitivities to those foods and inhalants to which they are exposed as they grow older. This is seen often in hay fever patients who develop new pollen sensitivities with age and continued exposure. The frequency and length of exposure required to make this happen and the question as to whether some allergens are more likely to induce sensitization than others (as is true with certain foods) await clearer solution.

Second, positive skin test reactions can increase or decrease or remain the same depending upon the following factors: (a) continued exposure, (b) no exposure, (c) after specific desensitizing treatment, and finally (d) perhaps as the result of a natural or spontaneous loss of reactivity coincident with or due to advancing age, as indicated in Table IV.

TABLE IV. POSSIBLE CHANGES IN POSITIVE SKIN TEST REACTION UNDER VARIED CONDITIONS

CONDITION	INCREASE	DECREASE	UNCHANGED
Continued exposure	Possible	Unlikely	Possible
Avoidance or no exposure	Unlikely	Possible	Possible
Treatment (hyposensitization)	Unlikely	Possible	Possible
Advancing age (natural factor)	Unlikely	Possible	Possible

METHOD OF STUDY

In an attempt to obtain answers to these questions, we reviewed the records of private patients seen in the past twenty-five years, choosing those who had been retested in order to secure the desired data and information. We realized at the outset that there were certain obvious drawbacks to such a study. Thus, if we wanted to compare the original test results with retests done a long time afterward, it justifiably might be said that we were not always using the same extracts in testing nor were the tests always performed by the same person even though all tests were done intracutaneously. The latter objection was avoided largely by selecting for final evaluation mostly the records of those patients who had both the original tests and the retests by the same person (V. M. H.). The objection as to the extracts perhaps is a more valid one, especially as applied to foods, which formed a large part of our retests. However, since all extracts were prepared and standardized in the same manner for skin test purposes, we felt that the percentage of error would be kept to a minimum. This was especially true of ragweed pollen which was the only inhalant used in our retest studies. Since this had been standardized by the total nitrogen method, and since we used the same strength for comparison, it was felt that the results would be reasonably reliable. Greater change probably was to be expected in retesting with food extracts because of their known variability; however, we tried to minimize this possible error by comparing the result of the original test with a retest done with the same concentration of extract. Furthermore, it was felt that these sources of error

would be reduced considerably by the large number of tests which were compared, using many different allergens rather than a single one; also perhaps, because it has always been our custom to retest all positives except marked ones at least one or more times, to make sure that it was a true or specific positive. We did this not only for the original test but with retests. By observing these precautions, we hoped to obtain perhaps in a general way sufficient information to be helpful to the allergist.

In general, the plan of investigation was as follows: We selected from our files the histories of those patients who had been retested at various intervals, and for reasons already mentioned; namely, either because of the recurrence of symptoms after a remission or of new symptoms or failure to respond to therapy. In the latter instances, the tests were done with the hope of finding new sensitivities to account for the recurrence. In other patients the retests were done to determine the effect of treatment (avoidance if a food, or specific injection treatment as with pollens). In either case the reaction originally obtained was compared with the retest result. In order to shorten what otherwise would be an enormous task, instead of comparing the retests with all the extracts with which patients usually are tested, we chose ragweed as the sole inhalant allergen because of the specificity of its extract and also because data as to contact and treatment were more easily available; also such food allergens as banana, chicken, chocolate, corn meal, egg, flounder, lobster, milk, orange, oyster, green pea, peanut, strawberry, tomato, and wheat to represent the more commonly eaten ones and artichoke, blackberry, chestnut, goose, green pepper, sweet potato, pumpkin, and rhubarb representing less commonly eaten ones.

By comparing the retest results with the original, we thus were able to determine whether there had been any change. Whenever possible, in those patients still under our care, we again reviewed the history with them to find out whether or not the patient had been eliminating the food from the diet completely. The data finally used, however, included only those active patients from whom histories as to food avoidance were considered reliable. In addition and whenever possible, retests were done upon any current patients who were eliminating foods completely for varying periods of time, to see whether this had any effect upon the skin test reaction. Furthermore, whenever new positives appeared in the retests, the history was again reviewed with the patient to determine whether there had been new or increased exposure to that allergen to account for the new positive. As a consequence, considerable valuable information was obtained.

To determine the effect of specific treatment on skin reactions, we also reviewed the histories of those hay fever patients who had ragweed pollen desensitization and in whom retests had been done at varying intervals. For many years, we regularly have retested those patients getting preseasonal treatment either both before and after the institution of pollen therapy (spring and fall, or each spring) or at varying intervals in the perennially treated cases. We thus were able to compare the original with the retest results (always using the same concentration of extract for testing) in patients who had been treated for long periods of time.

Finally an attempt was made through a special investigation (to be reported separately) to determine whether there is a tendency for a spontaneous or natural loss of reactivity of the skin coincident with advancing age. We tried to obtain this information by testing large groups of individuals (allergic and nonallergic) in various age groups with histamine in varying concentrations. In addition we reviewed our test cards for the incidence of positive skin reactions to the same food allergens according to the various decades beginning with the first and extending to the seventh or eighth if possible.

In order to prevent misinterpretation of our results especially when dealing with relatively small numbers of patients, all the figures presented in subsequent tables were subjected to expert statistical analysis,* the report being included with each table.

RESULTS

These are summarized in Tables V to X. For purposes of convenience and clarity, any changes in the tests will be recorded in degrees, each degree representing a unit of change, as indicated in Table V.

TABLE V. NEWLY ACQUIRED FOOD POSITIVES IN RETEST GROUP*

TOTAL NUMBER NEW POSITIVES		HISTORY OF CONTACT		NUMBER NEW POSITIVES ACCORDING TO YEARS BETWEEN TESTS		
COMMON	UNCOMMON	YES	NO	UP TO 5	6 TO 10	OVER 10
28	5	30	3	3	15	15

Extent of Change in Degrees

1° (from neg. to ±)	11
2° (from neg. to sl.)	19
3° (from neg. to sl. +)	2
4° (from neg. to mod.)	1

*Found in 15 patients out of total of 48 studied.

As indicated by clinical experience as well as from our questionnaire data, all allergists agree that patients can and do acquire new sensitivities. This likewise is substantiated by our data. Of the 48 retest patients reviewed, new positive reactions to different foods were found in 15 patients. The data obtained from a review of the histories with those patients and relating to their newly acquired sensitizations are summarized in Table V. This shows that 33 new positive reactions in varying degree appeared in the retests. Of these, 28 were to 10 commonly eaten foods and 5 to 5 uncommonly eaten foods. Of the 33, 11 were postive in 1 degree, 19 in 2 degrees, 2 in 3 degrees and 1 in 4 degrees. In other words, 22 of the 33 showed definite and substantial new positive reactions. It is of interest, too, to observe that in most instances (30 of 33) the newly acquired positive reactions could be substantiated by a history of new contact. Apparently, too, the longer the duration of contact, the greater the chance of sensitization, since more patients showed positive reactions when retested five or more years after the original tests than in the shorter period. In several patients, a history of excessive contact seemed to be responsible for or was followed by acquisition of new positives. This is exemplified in the following 2 case reports:

*We are deeply indebted to Dr. Hugh Hamilton, Professor of Psychology at Temple University, Philadelphia, for his valuable assistance both in obtaining our statistical results and in their interpretation.

CASE 1.—S. R., aged 31 years, seen in January, 1943, with seasonal hay fever, allergic rhinitis, and asthma. She was found to be fish-sensitive and therefore ate all kinds of fowl more often than before. In 1950 she became suspicious of symptoms following fowl ingestion. Retests at that time showed the following changes:

FOWL	SKIN TEST	
	1943	1950
Chicken	neg.	mod.
Duck	neg.	mod.
Goose	neg.	slt.
Turkey	neg.	mod.

CASE 2.—S. M., aged 17 years, seen in November, 1946, with asthma of one month's duration. Skin tests were positive to a few inhalants and foods but were negative to milk. In November, 1951, she developed tuberculosis for which antibiotic treatment was given. She drank 2 quarts of milk daily from November, 1951, to mid-June, 1952, when the amount was reduced somewhat. Wheezing attacks became recurrent after April, 1952. Retests done in August, 1952, now showed positive reaction to milk (slight in degree).

These two case reports, representative of other similar experiences, emphasize the important role of allergenic contact in the induction of sensitivity. This was verified further by the results of other investigations, to be reported later, which also show that allergic patients, when exposed to sufficient allergenic contact, are more easily sensitized than normals and are more likely to develop newly acquired sensitivities.

TABLE VI. EFFECT OF FOOD AVOIDANCE UPON RETESTS IN 46 PATIENTS*

AVOIDANCE	TOTAL NO. COMPARATIVE TESTS	REACTION UPON RETEST IN PER CENT		
		WEAKER	NO CHANGE	STRONGER
Complete	95	46.3	43.2	10.5
Incomplete	55	58.1	29.2	12.7
None	37	36.1	48.6	15.3

*P = 0.22 statistically not significant.

Table VI contains a summary of the data obtained in the clinical investigation of 46 patients ranging in age from 1 to 65 years at the time the original test was made. These patients had avoided different food allergens (common and uncommon) for varying periods of time; however, the table includes only those patients whose histories we considered reliable. Since multiple foods were used for comparison often in the same patient, a total of 187 comparisons were made with 15 different food allergens. Of this total, there was a history of complete food avoidance in 95; however, in 55 instances because the food was eaten occasionally we considered the avoidance as incomplete. Finally, in 37 instances the food was not avoided at all. Complete or incomplete avoidance was carried out for periods as short as six months to one year in 29 instances and as long as eleven years or more in 18.

The results obtained are not easy to interpret. Thus, if we contrast the change in skin reaction in those who ate the foods only occasionally or avoided them completely with that of those who continued to eat the positive-reacting

foods, only slight difference will be observed—thus reduction of the test to weaker or negative in the latter group was seen in a total of 36.1 per cent as contrasted with 46.3 per cent for the complete and 58.1 per cent for the incomplete. While the difference in percentage might seem greater than that in the column listed as "no change," such variation in so small a group is insufficient to be considered significant at least as indicated by our statistical analysis ($P = 0.22$).* This also is true of the analysis of the column marked "stronger"; here there was a slightly increased percentage of stronger reactions in the group without avoidance (15.3 per cent) in contrast especially with the complete avoidance group (10.5 per cent). While this might suggest an increase in sensitization from continued contact, this too was not statistically significant. On the whole, from the results obtained in these studies and analyses, it would appear that while avoidance of skin test positive-reacting foods at times might result in slight reduction in the skin test reaction, it is neither sufficiently frequent nor reliable to be depended upon clinically.

An effort also was made to analyze the relation of the degree of change in skin tests to the extent of avoidance to see if this would show anything significant. The results are shown in Table VII, which shows at once that many of the changes were of only 1 degree, which probably is small enough to be within the limits of technical error. If these are eliminated from consideration, there remains chiefly the group with 2 degrees of change. Here, too, the changes were slight—thus in the group with complete avoidance 29.6 per cent showed weaker reactions compared with 26.3 per cent with no avoidance, an almost negligible difference. Likewise, while the "no avoidance" group showed a slightly larger percentage of increased reactions than the others (5.3 per cent compared with 3.7 per cent and 2.6 per cent), suggesting possible increased sensitizations, these differences were quite small. Although there were too few cases in some categories to permit the computation of x^2, it seems obvious that these differences are not statistically significant.

Finally an attempt was made to see if the length or extent of avoidance would influence the skin test reaction. The results of this analysis are shown in Table VIII. Inspection and analysis of the data show that the change in skin reaction, whether weaker, stronger or the same, in the group with complete or incomplete avoidance retested within the one- to five-year period was not significantly different than that of those retested after six or more years of avoidance. Thus 50 per cent of the one- to five-year group had weaker reactions compared with 52 per cent of the "over six-year" group, 40 per cent of the former remained unchanged compared with 34 per cent of the latter and finally 10 per cent of the former became stronger as compared with 14 per cent of the "over six-year" group.

Upon the basis of the evidence presented, one must conclude that elimination of positively reacting foods from the diet of a patient may be followed at times by reduction in the skin test reaction, but this is likely to be slight

*Although the data in Table VI do not meet the assumptions upon which x^2 is based, it was considered the best available estimate for our purpose.

TABLE VII. FOOD AVOIDANCE—DEGREE OF CHANGE (IN PER CENT) IN 46 PATIENTS

DEGREE OF CHANGE	COMPLETE AVOIDANCE		INCOMPLETE AVOIDANCE		NO AVOIDANCE	
	WEAKER	STRONGER	WEAKER	STRONGER	WEAKER	STRONGER
1°	48.2	14.8	33.3	15.4	42.1	26.3
2°	29.6	3.7	38.4	2.6	26.3	5.3
3°	0	0	7.7	0	0	0
4°	3.7	0	2.6	0	0	0
Total comparative tests	54		39		19	

TABLE VIII. EFFECT OF LENGTH OF RETEST INTERVAL ON CHANGE OF FOOD REACTION

	REACTION CHANGE UPON RETEST IN PER CENT					
	1 TO 5 YEARS			6 OR MORE YEARS		
	WEAKER	NO CHANGE	STRONGER	WEAKER	NO CHANGE	STRONGER
Complete and/or incomplete food avoidance	50	40	10	52	34	14
Total comparative tests		100			100	

in degree. It would seem unwise, therefore, to depend upon such a reduction as a criterion of improvement in the patient's tolerance to that food and as an indication that food can be added back to the diet.

The data relating to the influence of ragweed pollen therapy upon the skin test reactions in hay fever patients are summarized in Tables IX and X. These include the findings in patients treated both perennially and preseasonally. The latter group was subdivided into those tested annually only and those in whom comparative tests were done before and after the season. Analysis of this data showed one thing not indicated in the tables but of interest in relation to the answers to our questionnaire; namely, that in a little more than one-third (36.4 per cent) of patients getting pollen therapy no change occurred in the skin test reaction and of the entire group few patients (1.1 per cent) developed a completely negative reaction.

As can be seen in Table IX, preseasonal pollen therapy apparently brings about little or no immediate change in the skin test reaction; thus in the group tested pre- and postseasonally in the same year the number of patients showing decrease in reaction at the end of the season was nearly the same (25 per cent) as those showing increases (30 per cent).

This lack of difference also was observed when we tried to compare the change in skin test reaction in those patients treated perennially with those treated preseasonally. Since we were interested in comparing only the effect of the method of treatment, we excluded those cases tested preseasonally and postseasonally during the same year (see third row of table) and compared our results in the perennial group with those of the preseasonal group retested at long intervals. While 48.3 per cent of the perennials had weaker reactions compared with 40.4 per cent of the preseasonals, this is counterbalanced by the fact that 22.5 per cent of the perennials had stronger reactions in contrast

to 18.0 per cent of the preseasonals. These differences were insufficient to be considered significant (P = 0.23). On the basis of this evidence, therefore, one can conclude that any change in skin reaction produced by pollen therapy does not depend upon whether the patient is treated perennially or preseasonally.

TABLE IX. RETEST RESULTS IN HAY FEVER PATIENTS RECEIVING POLLEN THERAPY

METHOD OF TREATMENT*	TOTAL NUMBER COMPARATIVE TESTS	REACTION UPON RETEST IN PER CENT		
		WEAKER	NO CHANGE	STRONGER
Perennial	89	48.3	29.2	22.5
Preseasonal tested long interval	89	40.4	41.6	18.0
Preseasonal tested pre- and postseason	20	25.0	45.0	30.0
Total tests†				
Number	198	84	72	42
Per cent		42.4	36.4	21.2

*For comparison between method of treatment and type of change P = 0.23 (not significant).

†For comparison between type of change among total tests P = < 0.01.

TABLE X. CHANGE IN SKIN TEST IN RELATION TO NUMBER OF YEARS TREATED—PRESEASONAL AND PERENNIAL

	NUMBER OF PATIENTS	NUMBER YEARS TREATED	
		1 TO 5	OVER 5
Decrease	79	38.0%	54.3%*
No change	63	42.6%	24.3%
Increase	36	19.4%	21.4%
Total comparative tests	178	108	70

*P = 0.04 (possibly significant statistically).

In order to determine the effect upon the skin test reaction of pollen treatment in general regardless of the method used, we compared the change in the retest results for the whole group including those treated perennially as well as those treated preseasonally and tested at long intervals. Of the total of 198 comparative tests 42.4 per cent showed a reduction, whereas 36.4 per cent showed no change, and 21.2 per cent had a stronger reaction. Since the extent of the reduction (42.4 per cent) was statistically significant (P = < 0.01), it indicates that in patients receiving pollen therapy a reduction in skin test reaction is more likely than is an increase, regardless of the method of treatment.

In addition, an attempt was made to analyze our data in both the preseasonal and perennial groups to see whether the duration or extent of treatment had any influence upon the change in skin test reaction. The results are shown in Table X. On the whole these show a fairly significant difference (P = 0.04). Thus, in the group treated more than five years, a larger proportion (54.3 per cent) showed a decrease in skin reaction than those treated one to five years (38 per cent). This would seem to indicate that long-continued pollen therapy in adequate dosage may bring about some reduction in the skin test reaction, at least it is more likely to bring about a decrease than is shorter treatment.

Since no reduction whatever occurred in more than one-third of patients and only 1.1 per cent developed a completely negative skin reaction after treatment, one must conclude that pollen therapy, regardless of the method (preseasonal or perennial), has only a slight reducing effect upon the skin test reaction and then only after a long period.

Finally, there remains for consideration the fourth possible influence upon skin test reactions—namely, the physiologic factor of advancing age. The results of our investigation of the latter factor, to be reported subsequently, in a general way confirmed our clinical impression that skin reactivity lessens with advancing age. Thus, we found that the incidence of positive skin reactions was greatest in the first decade of life, decreases slightly up to the age of 50 years, and declines sharply thereafter. This was substantiated further by our supplementary testing with histamine which showed that skin reactivity definitely lessens after 50, in nonallergic and allergic individuals alike.

CONCLUSIONS

As indicated by a review of the literature as well as from analysis of questionnaire data, it has been shown that the opinion of practicing allergists is divided as to whether skin test reactions change and as to the reasons for such change. From the results of our investigations into this problem the following conclusions seem justified:

1. Patients can and do acquire sensitization to new food allergens. This tendency is enhanced by continued or prolonged contact with these agents since sensitization as indicated by positive skin test reactions occurred more frequently in relation to commonly eaten foods than to those uncommonly eaten.

2. Once skin sensitization occurs, as evidenced by a specific positive skin test reaction, it changes very little either as the result of allergen avoidance or of treatment. Thus avoidance of foods for varying periods of time as well as specific pollen therapy as a rule produced little or no significant change, except, as in the case of pollens, after long-continued treatment (five or more years). Therefore, one should not rely upon a reduction in skin test reaction as a criterion of improved tolerance to permit readdition of a food or as a guide in pollen therapy.

3. Skin test reactions may change with advancing age, especially after 50, because of a lessening of skin reactivity.

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ALLERGY AS A CAUSE OF GLAUCOMA

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GLAUCOMA causes at least 12 per cent of the blindness which occurs each year in the United States. In spite of this significant fact, little is actually known about the etiological factors which produce this crippling disease. The most puzzling form of glaucoma appears to be the chronic, simple, congestive type manifested by increased ocular tension without other abnormal pathologic findings. It is believed by most authors that vascular changes are responsible for the increased tension, but the unanswered question has always been: "What initiates these local vascular changes?" It is the purpose of this discussion to present a patient with recurrent, simple, congestive glaucoma who appeared to be getting progressively worse until brought under allergic management.

CASE REPORT

Mr. W. M., a 64-year-old white man, was first seen on March 2, 1953. He gave a history of recurrent pain in and around the left eye for the past five years, usually coming on about two hours after meals. The eye would tear and usually become red. He often noted that he would become bloated with gas before the eye symptoms developed. The digestive attacks lasted one to three hours, but might be relieved by the eructation of large amounts of gas. He had occasional bouts of constipation and very rarely nausea or vomiting. At times antacid pills relieved the gastrointestinal and eye symptoms.

Allergic history disclosed that the patient had had two bouts of asthma during the past six years, each attack lasting several weeks. He never had hay fever, hives, eczema, migraine, or perennial rhinitis. The family history was negative for allergy, as far as could be ascertained. System review was essentially negative except for a chronic nondischarging perforation of the left eardrum which had been present since childhood. The patient lived in a 26-year-old, one-story house where he had two canaries for pets and had never observed any dust precautions. He ate a well-balanced diet, but noted that onions "repeated" on him and that oranges invariably left a bitter taste in the mouth.

Physical examination was essentially negative except for moderate obesity. Complete blood count, urinalysis, sedimentation rate (Wintrobe), and blood sugar were all normal. Complete skin testing revealed slightly positive reactions to only the following: dust, hormodendrum, cow, horse, sisal, shad fly.

Consultation with the referring ophthalmologist revealed that the patient had been having recurrent attacks of glaucoma in the left eye since 1946. He has had several attacks since then, each associated with increased ocular tension ranging from 35 to 54 mm. Hg. Therapy for each attack consisted of applying .25 per cent eserine ointment two to four times daily until the symptoms were relieved. Occasionally it was also necessary for him to have injections of morphine to relieve the pain. Each acute episode lasted from several hours to two weeks. The patient's vision as determined by visual field and tangent screen studies was not affected during any of the attacks. During the month prior to his initial visit to the office, he had more frequent attacks. These were relieved at first by eserine but eventually became refractory to miotics and recurred daily. During this same period he also had an increased amount of gastrointestinal distress and, because of this, his ophthalmologist believed that the two conditions might be connected. In view of the associated symptoms, he was advised to have an allergic investigation. Because of the steady progression of his disease, he readily accepted the suggestion.

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From the skin-testing results, it did not appear that any of his mild reaginic sensitivity was responsible for his symptoms. The patient therefore was asked to keep a food diary to see what further information could be elicited regarding food sensitivity. He noted that he had trouble after eating peaches, mayonnaise, and green peas. The attack after eating peas came within the next two hours. With the foregoing facts and his previous food history in mind, the patient was put on an elimination diet in which the following foods were avoided: peas, beans, nuts, mustard, mayonnaise, oranges, pitted fruits, (peaches, plums, apricots, and cherries). Beans, nuts, mustard, plums, apricots, and cherries were eliminated along with peas, peaches, and mayonnaise as these foods are all members of the same food family (legume), and are closely related antigenically. Mayonnaise was eliminated from his diet since it usually contains mustard. He began to feel better almost immediately. The attacks of ophthalmic pain and gastrointestinal distress disappeared. When the patient was seen one month later, he stated that he had not felt so well in years. On questioning eight months later, he still continued to feel exceedingly well. Several months ago, he drank a glass of orange juice and shortly thereafter noted discomfort in both his eyes and in the gastrointestinal tract. Recently he tried eating peas and was most uncomfortable as he quickly filled up with gas. The symptoms subsided on each occasion as soon as he went back on his elimination diet. In view of this information, it would appear that either oranges or any member of the legume family could produce a flare-up of his glaucoma or could cause gastrointestinal distress. In fact, as previously stated, these two reactions very frequently occurred simultaneously.

DISCUSSION

The concept that allergy can cause glaucoma is not new. As early as 1925, Brown[1] reported on the eye findings in both experimental and human serum sickness. Although he did not do tangent screen studies or measure eye pressures, it seems quite clear, from his clinical findings, that several of his patients were having acute congestive glaucoma as a part of their serum sickness. In 1930, Friedenwald[2] removed the eyes from 11 patients with glaucoma and made an extract from the aqueous humor of these patients. He reported the production of urticarial responses after injection of this extract intracutaneously into these same patients, but could not duplicate this result by the injection of either saline or the extract of the aqueous humor from nonglaucomatous patients. At about this time, Friedenwald and Pierce[3] also produced increased ocular tension by the injection of histamine into the vitreous humor of animal eyes. In 1933, Duke-Elder[4] stated that he thought it "possible for histamine or the H substance of Lewis to produce localized vascular changes in the eye which could lead to glaucoma." A year later, Evans and Evans[5] described glaucoma as acute angioneurotic edema of the eye. Duggan[6] in 1945 and Hansen[7] in 1950 each wrote rather extensive monographs on the subject of allergy and its relationship to diseases of the eye. Both authors thoroughly reviewed the literature but presented no actual cases for discussion. They each left a definite impression, however, that allergy could cause glaucoma. In 1947, Behrens and his group[8] presented three cases of glaucoma caused by various food allergies. These patients were well-worked up from the ophthalmological point of view, including numerous visual field studies and pressure readings before and after the institution of allergic management. The information regarding the allergic phase of their illness, however, was most sketchy. None of these three individuals had allergic investigations, and the only clues to allergic diagnosis were elicited by pulse studies done according to the method

of Coca. These patients were followed for many months after institution of their diets, and all showed continued improvement even without the use of local medication. There seems little doubt that the glaucoma in these subjects was caused by food allergy, but unfortunately no attempt was made to feed any of these foods a second time to see if the glaucoma could be reactivated. Interestingly enough, just as our patient lost his gastrointestinal symptoms following institution of allergic management, one of Behrens' patients noted a similar clearing of long-standing gastrointestinal complaints after his glaucoma had responded to treatment.

Recently, a case of simple congestive glaucoma was discussed by Pavisic[9] in a Jugloslavian medical periodical. The glaucoma occurred as a part of a generalized systemic reaction to sulfonamide. This same reaction was produced by sulfonamide on two different occasions one year apart, so there was little doubt that the reaction was a specific one.

One of us (D. M.) several years ago observed a 27-year-old man who had developed acute congestive glaucoma. The patient was a very heavy wine drinker and on skin testing amongst several positive responses was found to have a large reaction to grape. He was told to stop drinking wine and the glaucoma cleared.

It would appear that certain blood vessels of the eye can act as an allergic shock organ, thereby producing increased ocular tension. This phenomenon seems more likely to occur if allergy is concomitantly causing active symptoms in some other organ of the body. It is regrettable that masked feedings could not have been performed in order to establish the validity of the diagnosis more accurately. Unfortunately when dealing with private patients, it is not always possible to carry out all the experimental procedures one might desire. It is hoped, however, that the presentation of this patient and the brief review of the literature will help to stimulate more investigative studies of allergy and its possible relationship to the etiology of simple, recurrent, congestive glaucoma.

SUMMARY

A case of simple, recurrent, congestive glaucoma is discussed. The patient was relieved of both glaucoma and gastrointestinal symptoms by the control of various food allergies.

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CLINICAL EVALUATION OF SUSTAINED-RELEASE ANTIHISTAMINE (CHLORPROPHENPYRIDAMINE) IN HAY FEVER

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A LARGE proportion of patients with hay fever fail to seek treatment until the season is well under way and their symptoms have become severe. As a result, antihistamines have become well-established adjuvants in managing such patients by augmenting desensitization and by providing symptomatic relief. Even though these drugs are of doubtless value, however, their use is attended by three main shortcomings: limited usefulness; short duration of action; side effects of drowsiness and dizziness.

Recently I obtained for investigational use chlorprophenpyridamine maleate in a new oral dosage form which conceivably could reduce or eliminate these shortcomings. Called sustained-release medication, this dosage form consists of a capsule containing three average doses of the drug prepared in the form of numerous micropellets, some of which are coated, some uncoated. As soon as the capsule disintegrates after its ingestion, the uncoated pellets release a sufficient amount of drug to produce a therapeutic effect. The coated micropellets, coated with varying thicknesses of a digestible film, then maintain the initial therapeutic effect over a period of approximately twelve hours by gradually releasing additional amounts of drugs. Since drug release is continuous as well as gradual, instead of intermittently or all at once, this dosage form might be expected to produce a smoother drug action instead of high and low points of drug action which come with repeated single doses of drugs in currently available oral dosage forms. Moreover, since side effects are believed related to excessive therapeutic peaks, sustained-release antihistaminic capsules, by their smooth action, might reduce drowsiness, dizziness, and other annoyances of antihistamine therapy. This study was therefore undertaken to determine whether such capsules will provide a long-lasting antihistaminic effect and whether their use will influence the incidence of side effects. To do this, we administered the new preparation to 128 allergic patients, predominantly hay fever sufferers, and compared the results with those obtained when we gave the patients the same drug in standard tablet form.

MATERIAL

All but two of the 128 patients in this series were seen in private practice during August through September, 1953; the other 2 were seen in a clinic. The group consisted of 69 men and 59 women whose ages ranged from 10 months to 78 years: 10 per cent were under 10 years; 30 per cent were between 10 and 19 years; 45 per cent were between 20 and 40 years; 15 per cent were over 50 years of age. Clinical characteristics of the group are given in Table I.

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TABLE I. CLINICAL CHARACTERTISTICS OF PATIENTS RECEIVING CHLORPROPHENPYRIDAMINE MALEATE

DIAGNOSIS	NUMBER OF PATIENTS	CONCURRENT DESENSITIZATION	AVERAGE NUMBER OF YEARS ALLERGY RECURRED
Hay fever (fall pollinosis)	98	48	12
Hay fever with allergic asthma	15	7	16
Hay fever with urticaria	4	1	3
Hay fever with urticaria and allergic asthma	2	2	11
Vernal conjunctivitis	1	-	-
Allergic rhinitis	6	3	7
Urticaria	2	-	2*

*Includes one whose symptoms began this year.

Twenty-three patients, 9 of whom experienced their first attack of hay fever this year, had not previously been treated for their allergies. Of 105 patients who had previously received ragweed-desensitizing injections, antihistamines, or a combination of desensitizing injections and antihistamines, 35 had obtained adequate symptomatic relief so that they had been comfortable; 25 had obtained fair relief; 45 patients, many of whom did not seek treatment until after their symptoms had become acute, had obtained little or no relief.

METHOD

Patients or parents of child patients who showed promise of cooperation were told of our plan for evaluating two antihistaminic preparations and were asked whether they would be interested in participating. To those who were, we gave a week's supply of the antihistamine, chlorprophenpyridamine maleate, and a card on which they were asked to estimate and record, at the end of each day for one week, their degree of hay fever discomfort as well as any other complaints—side effects—that they experienced while on the medication.

At their initial visit, patients were given the drug in either tablet or sustained-release capsule form: part of patients were started on tablets, part on capsules. Those who received tablets were told to take one tablet, which contained 4 mg. of chlorprophenpyridamine, every four hours; those who received capsules were told to take 1 capsule every twelve hours, that is, 1 capsule in the morning (8 A.M.) and 1 capsule in the evening (8 P.M.). Each capsule* contained 12 mg. of the drug prepared so that 4 mg. would be released soon after the capsule was taken, and so that the remaining 8 mg. would be released gradually and continuously over the next eight to ten hours.

Patients were seen at the end of a week, and those who had been started on tablets were switched to capsules during the second week, and vice versa. Nine patients who had been started on capsules were switched to the drug in a layered enteric-coated tablet that contained 8 mg. prepared so that 4 mg. would be released soon after the tablet was taken and the remaining 4 mg. would be released all at once approximately four hours later. They were told to take one enteric-coated tablet, twice daily; that is, one in the morning, and one in the

*Supplied for investigational use as "Teldrin" *Spansule* capsules by Smith, Kline & French Laboratories, Philadelphia, Pa.

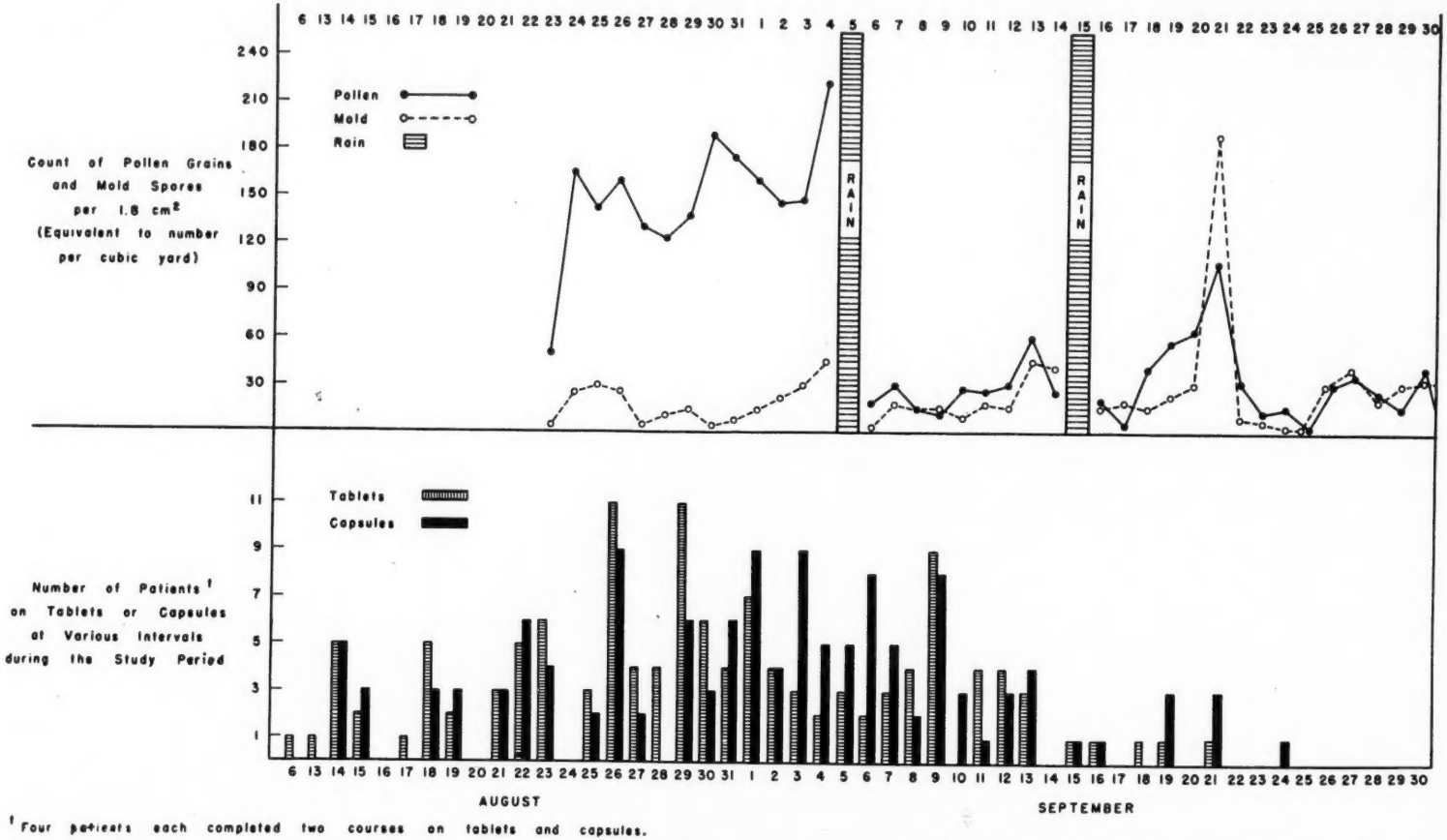
Count of Pollen Grains and Mold Spores per 1.8 cm² (Equivalent to number per cubic yard)
Pollen
Mold
Rain
RAIN
RAIN
Number of Patients[1] on Tablets or Capsules at Various Intervals during the Study Period
Tablets
Capsules
AUGUST
SEPTEMBER
[1] Four patients each completed two courses on tablets and capsules.

Fig. 1.—Record of pollen and mold count and rainfall in Reading, Pa. (upper) in relation to number of patients on tablets or capsules at various intervals during the study period (lower).

evening. Fifty-four patients continued to receive an intracutaneous injection of a histamine-protein antigen complex once a week; six others received a Histadyl injection once a week; and one patient occasionally used Privine for relieving nasal stuffiness.

After the patients had been on the drug for two consecutive weeks, either tablets or sustained-release capsules, they were interviewed to learn whether one preparation provided more symptomatic relief; whether they preferred one preparation to another and why; how long they thought it took for each preparation to take effect and how long that effect lasted; whether one preparation caused more side effects; whether the patients worked in or lived in an air-conditioned or an air-filtered environment; whether they had taken a vacation while on the drug and whether the vacation locale had influenced their symptoms.

To balance the variation that might result from changing pollen count, mold spore count, humidity, and rainfall, we made certain that both preparations were usually under test at the same time. Moreover, counts of pollen and mold spores were taken daily, and a record of rainful was kept throughout the hay fever season so that we could weigh these factors when interpreting our results. Fig. 1 shows these data as well as their relation to the distribution of treatment between tablets and capsules.

RESULTS

A summary of the degree of symptomatic relief obtained with chlorprophenpyridamine prepared in each of three different dosage forms is presented in Table II. Only one patient was lost from the experiment; however, two patients took only capsules because their symptoms were completely relieved, and they required no further medication. One patient with chronic urticaria was started on capsules and later reported that his hemorrhoids, which have bothered him for more than twenty years, had disappeared. Since he believed that the capsules were responsible for this relief, he would not accept medication other than the capsules.

Of 127 patients who took the drug in sustained-release capsules, 100 obtained excellent symptomatic relief of hay fever distress; 24 obtained moderate relief; and 3, fair relief. These same patients, with three exceptions mentioned before, completed a week's treatment on the tablets or the enteric-coated tablets. Eleven of the 115 patients who took the drug in tablet form reported excellent symptomatic relief; 39 reported moderate relief; 41, fair relief; and 24 reported little or no symptomatic relief. One of 9 other patients who took the drug in enteric-coated tablets obtained excellent relief; 4, moderate relief; 2, fair relief; and 1, no relief. It should be borne in mind that the majority of these patients had had hay fever for many years, and from their previous experience with various remedies they should qualify as competent subjects for judging the usefulness of a preparation for relieving hay fever.

Analyses of the data collected during the interviews showed that the patients preferred taking the capsules because they obtained more and longer lasting relief with the capsules than with tablets. In addition, they liked the convenience that results from their not having to take, or remember to take, frequent doses

TABLE II. DEGREE OF SYMPTOMATIC RELIEF PROVIDED BY THE DRUG IN EACH OF THREE DOSAGE FORMS

	EXCELLENT	GOOD	FAIR	POOR	TOTAL
Tablets	11	39	41	24	115
Enteric-coated tablets	1	4	2	2	9
Sustained-release capsules	100	24	3	-	127

during the day. Most patients commented that since taking the capsules they were better able to get a good night's rest, and that they no longer had to use a gamut of nasal decongestants. As might be expected, patients with asthma complicating their hay fever symptoms benefited mostly in relation to hay fever symptoms. Although these patients were made more comfortable, it is doubtful that the medication relieved their asthma to any extent. Only 5 patients, who obtained the same beneficial results with tablets as with capsules, had no preference. Four other patients preferred taking tablets.

Average onset of action, as estimated by the patients, was as follows: tablets approximately forty-five minutes; enteric-coated tablets, one hour; capsules, slightly more than one hour (1.2 hours). Duration of action was judged to last about four hours with tablets; slightly more than seven hours with enteric-coated tablets; more than ten hours with capsules.

These results indicate that the antihistaminic effect of one sustained-release capsule will last throughout the day and is approximately equivalent to three 4 mg. tablets taken at four-hour intervals. Moreover, since its effect is prolonged, one sustained-release capsule taken an hour or two before bedtime provides, in most cases, a protective action that lasts throughout the night. Apparently, the sustained effect resulting from taking a capsule in the evening accounts for the patients' comments on sleeping better while taking capsules.

Side effects, except for drowsiness, did not occur to any extent. The incidence of drowsiness—16 per cent with tablets, 12 per cent with capsules—was essentially the same with both preparations; however, the degree of side effects was less with sustained-release capsules than with tablets. One patient developed a papillary dermatitis while taking the drug in each dosage form; one developed a rash only while on capsules. Only 1 of 8 patients who complained of dizziness while taking tablets became dizzy on capsules. The incidence of headaches and nervousness is of no significance, and apparently is not related to the drug inasmuch as the patients' complaints stopped when their medication was changed from tablets to capsules, and vice versa. Table III is a summary of the side effects resulting from the drug when given in three dosage forms.

DISCUSSION

The present investigation was carried out to determine the relative usefulness of a new dosage form of chlorprophenpyridamine maleate, an antihistaminic with a record of low toxicity[1] and established clinical efficacy.[2, 3, 4] The results, based on patients' evaluation, indicate that this antihistaminic is considerably more effective when given in sustained-release capsule form than in tablet and delayed-action tablet forms. Moreover, the degree of side effects was found to be less with sustained-release capsules. Apparently, the gradual

and continual release of antihistamine afforded by the new dosage form eliminates sharp therapeutic peaks and reduces the resultant annoying side effects. From these results, it is believed that the sustained-release antihistaminic capsule is the most useful antihistaminic preparation currently available as adjuvant therapy in treating hay fever.

TABLE III. SUMMARY OF SIDE EFFECTS RESULTING FROM THE DRUG GIVEN IN EACH OF THREE DOSAGE FORMS

	TABLETS			SUSTAINED-RELEASE CAPSULES			LAYERED ENTERIC-COATED TABLETS		
	SEVERE	MODERATE	MILD	SEVERE	MODERATE	MILD	SEVERE	MODERATE	MILD
Drowsiness	1	15	3		4	11			1
Dizziness	1	5	2			1			
Nausea		1	5		2	2			1
Headaches		1	6		1	4			
Coughing		1	2			2			
Restlessness			3			4			
Rash			1			2			
Dryness of nose and throat			5						
Pruritus			2						

In addition, the new dosage form offers the considerable advantage of convenience to busy, preoccupied, and forgetful patients in that it frees them from the burden of taking medicine at frequent intervals during the day. When taken in the morning, one capsule provides an antihistaminic effect that lasts throughout the day; when taken in the evening, one capsule provides the same effect that lasts throughout the night.

SUMMARY

One hundred twenty-eight patients with allergic disorders, predominantly hay fever, were treated with chlorprophenpyridamine maleate in each of three dosage forms: tablets, enteric-coated tablets, and sustained-release capsules. Patients greatly preferred the capsules because of their superior effectiveness and their long action, which eliminates the need for frequent doses throughout the day. Except for drowsiness, side effects were minimal. The incidence of drowsiness was essentially the same with tablets and capsules, 16 and 12 per cent, respectively; however, the degree of drowsiness was less with the capsules.

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PULMONARY FUNCTION IN BRONCHIAL ASTHMA

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IN THE past thirty years, excellent reports dealing with pulmonary function have appeared. The earlier articles were concerned chiefly with studies of lung volume, ventilation, and analysis of the alveolar air in normal subjects and in patients with a variety of lung disorders.[1-7] The information gained was applied to patients about to undergo artificial pneumothorax, thoracoplasty, lobectomy, or pneumonectomy in an attempt to predict the alterations in lung function following such measures. In addition, it was soon possible to describe fairly characteristic patterns of respiratory function for pulmonary fibrosis, emphysema, and pneumoconiosis. Among a number of protocols in these studies, were found some interesting data dealing with bronchial asthma, most of which were incidental to these investigations. The newer techniques of cardiac catheterization have proved to be most useful for the understanding of both respiratory gas exchange[8] and the lesser circulation, especially as this last is affected by chronic lung disease. More recent studies of the compliance and viscance of the lung and thorax have contributed to a better understanding of the factors concerned with the mechanics of breathing.[9-11] Bronchial asthma gives rise to alterations in the lung volume and its subdivisions, faulty distribution and "mixing" of the inspired air, and a consequent impairment in the exchange of lung and blood gases.

We have included in this paper some of the more recent and pertinent literature concerned with assessing respiratory function in bronchial asthma and have described those procedures which we have found most useful in the study of patients with bronchial asthma. The terminology used is shown in Fig. 1. A detailed description of methods, standards for comparison, and prediction formulas may be found elsewhere.[12-14]

Tests of pulmonary function may be classified as follows: (1) measurement of the lung volume and its subdivisions; (2) tests of breathing capacity: the timed vital capacity and the maximal breathing capacity; (3) the distribution and "mixing" of the inspired gas in the lung; (4) the arterial blood gases; (5) tests of over-all pulmonary function such as the volume of oxygen removed per liter of air breathed and the saturation rate. It is self-evident that measurements of lung function will vary depending on the severity of the disease at the time of testing. Most workers have made studies on asthmatic patients during a remission so that the striking changes which one would expect to see during an attack are rarely noted. For this reason, the reported figures may not be at all representative of severe asthma, and, furthermore, the abnormality described may well be caused by changes in the lung other than those which characterize uncomplicated bronchial asthma.

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Comparison of results obtained in asthmatic subjects with the values which would be expected were the subject in perfect health is of less value than one might expect. The range for the predicted normal values is large and they cannot always be regarded as reliably indicating what would be normal for the particular individual under consideration. More information can be obtained as a rule by tests made in varying stages of the patient's illness.

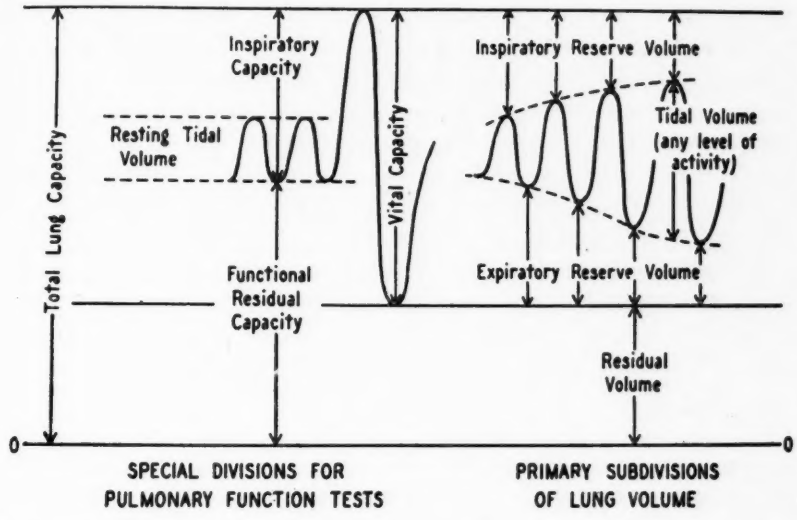

Fig. 1.—The subdivisions of the lung volume. (From Fed. Proc. 9: 602, 1950.)

THE LUNG VOLUME AND ITS SUBDIVISIONS

The oldest objective test of ventilatory function is the vital capacity, and because of its simplicity it has been used widely. The vital capacity measures the maximal volume of air that can be expired following a maximal inspiration. It is noteworthy that the vital capacity was in use for about fifty years before much was written concerning its application to bronchial asthma. However, prior to World War I, interest in this subject began with the publication of articles[1, 15] dealing with lung function in which it was observed that the asthmatic attack was attended by a decrease in the vital capacity. This was supported by subsequent reports[4, 5, 16-19] which also indicated that a number of patients had impaired vital capacities even when free of symptoms; this was generally ascribed to the development of pulmonary emphysema. Studies dealing with the vital capacity in relation to the total lung volume began to appear about 1930[2, 3, 5] with the wider application of pulmonary function tests in cardiopulmonary disease. Considerable time was given over to the development of normal standards and to the formulas for prediction of expected values. More recently a number of comprehensive papers[20-24] have appeared in which pulmonary function studies were carried out in asthmatic subjects who were free or almost free of symptoms. These investigations added little to what was

already known about the vital capacity except to call attention again to the significant reduction that is frequently seen in asthmatic subjects ostensibly free of signs and symptoms.

The inspiratory capacity and the expiratory reserve volume, often referred to as the fractions of the vital capacity, may be measured directly from spirographic tracings. Little data is available in asthma and in other pulmonary conditions, perhaps because of the "difficulty in interpreting changes in these two fractions."[14] Even in well-controlled experiments these fractions, particularly the expiratory reserve volume, tend to be quite variable. Measured from the resting midcapacity or resting expiratory level, the inspiratory capacity is the maximal volume of air that can be inspired. This makes up about 75 to 80 per cent of the vital capacity in normal individuals. The maximal volume of gas that can be expired from the resting expiratory level is the expiratory

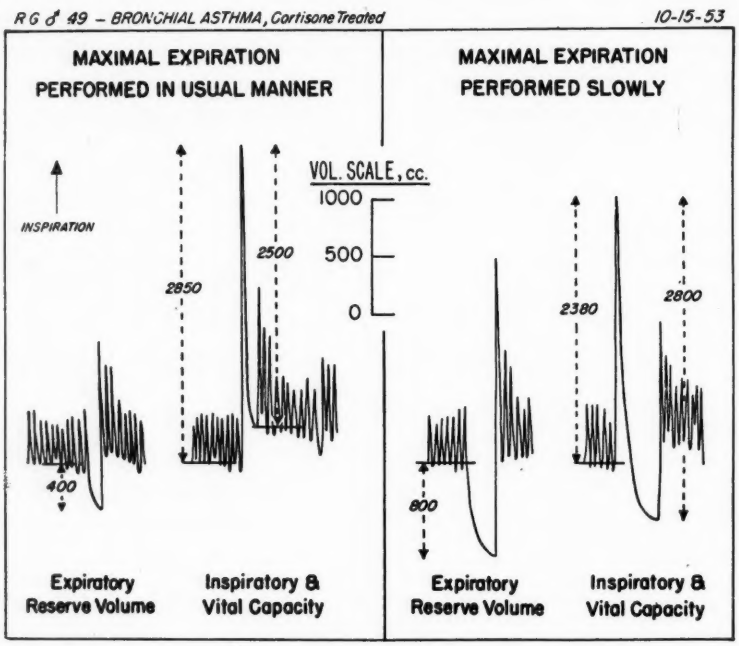

Fig. 2.—Spirogram in bronchial asthma with maximal expiration performed rapidly and slowly.

reserve volume, and this is 20 to 25 per cent of the vital capacity. Along with the decrease in vital capacity in asthma, the expiratory reserve volume and even more so the inspiratory capacity, are also decreased. In patients with asthma or emphysema, when the fractions of the vital capacity are recorded separately, it may be found that the sum of these may exceed the volume of the vital capacity performed in the usual manner.[2, 22] This discrepancy, evident when the vital capacity is measured in these two different ways, has been attributed to the loss of pulmonary elasticity[2] or "trapping" of air in certain portions of the lung. On the other hand, when a patient with asthma or emphysema is instructed to perform a vital capacity or expiratory reserve volume *slowly*,

significantly larger volumes are often produced[25] (Fig. 2). We have assumed that, upon deep inspiration, narrowed or obstructive airways within the lung open and poorly ventilated and partially collapsed areas of the lung fill. With forceful and rapid expiration, the well-ventilated areas empty promptly, relieving those forces which have kept the airways to the poorly ventilated portions open. These again close so that the contained air cannot escape. When the expiration is slow, on the other hand, these areas have sufficient time to empty before the airways close.

The spirogram does not give information concerning the residual volume for the measurement of which special techniques are required.[13] This volume is that which remains in the lungs after forced expiration and normally makes up 20 to 25 per cent of the total lung volume. The sum of this volume and the expiratory reserve volume is the functional residual capacity. The functional residual capacity and the residual volume may increase considerably with age, and in some older individuals who are otherwise well the residual volume may be 40 to 50 per cent of the normal total lung volume.[14] The residual volume and functional residual capacity are found to be markedly increased in bronchial asthma during paroxysms.[26] However, in a careful study of 10 asthmatic subjects comparatively free of symptoms, the residual volume was normal even though other significant abnormalities in pulmonary function were present.[20]

The sum of the vital capacity and the residual volume is the total lung capacity. Absolute values for this volume show a wide range of variation, and unless a patient exhibits marked deviation, it may be difficult to recognize an abnormality. Furthermore, even in healthy subjects the total lung capacity may vary from the estimated normal by plus or minus 15 to 20 per cent.[14] The total lung capacity may be estimated by dividing the vital capacity by 0.80 for the age group 15 to 35 years, by 0.76 for the group 35 to 49 years, and by 0.692 in the group over 50 years.[13] Because of the phenomenon shown in Fig. 2, rather than the vital capacity, we prefer to use the sum of the expiratory reserve volume and the inspiratory capacity for this estimate.

Some workers have found little or no deviation from normal values for the total lung capacity in bronchial asthma,[4, 20] whereas others have reported some increase.[22-24] In a group of patients with emphysema and some degree of asthma, the increase in the ratio of the residual volume to total lung capacity correlated very well with the degree of disability. As the total capacity in most of these patients was normal,[4] this correlation was almost entirely dependent on an absolute increase in the residual volume.

BREATHING CAPACITY

Though study of the lung volume and its subdivisions, especially the vital capacity, frequently reveals significant alterations in asthma and emphysema, information of much greater value may be afforded by assessing quantitatively the volume of air that moves into and out of the chest in a unit of time. The volume of air breathed per minute divided by the number of respirations is the average tidal volume. The gas that enters the alveolar spaces and participates in gas exchange is the effective tidal volume and is calculated by sub-

tracting the dead space volume from the average tidal volume. The dead space has been estimated to be 150 c.c. in men and 110 c.c. in women.[13] In bronchial asthma the change in tidal volume and respiratory rate may be quite variable, and their product, the minute volume, is usually maintained at normal or, as most workers have found, at somewhat elevated levels.[21, 22] For the most part, however, the resting ventilation has little value in assessing the degree of the ventilatory defect. On the other hand, the patient's capacity to move air in and out of the chest rapidly is of great significance. Of the methods for measuring this, the oldest and most widely used is the maximal breathing capacity. The maximal breathing capacity is performed with maximal voluntary effort over a period of 15 to 30 seconds, and the volume of air breathed is expressed in liters per minute. The subject is continually urged to breathe as hard and as fast as he can but is allowed to choose his own respiratory depth and rate. The average normal value for men is reported to be 154 liters and for women 100 liters per minute.[27] Considerable variation in the maximal breathing capacity has been noted even in normal subjects in whom a deviation by as much as 25 to 30 per cent of the mean group values has been reported. To be significantly abnormal, the maximal breathing capacity, therefore, must be considerably reduced. In bronchial asthma the maximal breathing capacity has often been found to be reduced out of proportion to the reduction in vital capacity,[20-24, 28, 29] and the longer the duration of asthma, the less the maximal breathing capacity.[23] This was not an unexpected finding. Gaensler,[28] comparing the vital capacity and the maximal breathing capacity in 9 asymptomatic patients with asthma, found the vital capacity reduced by 17.5 per cent as compared with a reduction in maximal breathing capacity of 58.8 per cent. It has been suggested[14] that some less stressful procedure might well replace the maximal breathing capacity, and in this we are heartily in accord. The timed vital capacity seems to satisfy this need as this correlates well with the maximal breathing capacity.[30, 31]

THE DISTRIBUTION AND "MIXING" OF THE INSPIRED GAS

The lungs of normal subjects have been shown to be unevenly ventilated and this has been attributed to differences in the way in which various regions of the lung are ventilated.[32] With fractional analysis of alveolar air and employing a single inspiration of a hydrogen mixture, Roelsen[6] showed that patients with bronchial asthma and pulmonary emphysema had considerably greater variation in the composition of alveolar gas than did normal subjects. Using a somewhat different approach, Birath[33] found that there was impaired intrapulmonary mixing in patients with bronchial asthma similar in most respects to that seen in pulmonary emphysema. These methods were time-consuming and complex and were not well-adapted for routine use. In about 1940, a relatively simple open circuit method was described which could be used for the determination of intrapulmonary mixing as well as for the determination of the residual volume.[34, 35] This method has received widespread acceptance and is now in general use. In brief, the subject breathes oxygen for seven minutes, following which an alveolar sample is delivered and analyzed for nitrogen.

Normally at the end of this washout or emptying period the concentration of nitrogen in the alveolar gas is less than 2.5 per cent. If distribution of gas within the lung is impaired, the concentration of nitrogen in the alveolar sample is high. Though relatively simple and practical, the method has been criticized because it does not take into account the volume breathed or the functional residual capacity of the patient. Some emphysematous subjects, for example, who hyperventilate, will reduce the alveolar nitrogen concentration at the end of the seven-minute period so that the test may fall within the normal range.[14] Conversely, it is possible that the inhalation of oxygen by depressing respiration may tend to exaggerate the difference between normal and abnormal subjects.[13, 36] Nevertheless, the test is clinically useful, especially in the diagnosis of pulmonary emphysema. Using the open circuit method, Baldwin found a mean value of 4.5 per cent nitrogen in 10 asthmatic patients even though they were relatively free of symptoms. Interestingly none of the patients had an increase in the residual volume to total lung capacity ratio, nor was arterial oxygen unsaturation present. Likewise other workers have found abnormally high levels of alveolar nitrogen in asthma by this method.[21-23]

Reinvestigating the uniformity of alveolar gas in normal subjects, Fowler[32] devised the single breath test, and with this technique he was not only able to confirm the presence of uneven ventilation in normal subjects, but showed that this occurred on a regional basis. Essentially the method consists of having the subject expire fully and then inspire oxygen maximally followed by a forcible expiration. Using special flow and nitrogen meters, the expired gas is continually analyzed for nitrogen concentration. The rise in concentration of nitrogen in that portion of alveolar gas, amounting to 500 c.c., which follows the first 750 c.c. expired, is the uniformity index and in normal subjects does not exceed 2 per cent. This index was 3 to 4 per cent in patients with uncomplicated asthma and up to 10 per cent in patients with marked pulmonary emphysema. The uniformity index, derived from the single breath test, was compared with the open circuit method in 77 patients with miscellaneous pulmonary disease.[37] Seventy-eight per cent of these patients were abnormal as judged by the uniformity index, whereas there were only 32 per cent by the other method. Of significance were the 17 patients with asthma under the age of 50 of whom 24 per cent were abnormal by the open circuit method as compared to 76 per cent with the single breath test. In a more recent article these workers again compared these two indices.[22] With the open circuit method 5 of 19 asthmatic subjects were found to have an abnormal alveolar nitrogen. Eighteen of these patients were retested by the single breath test, and abnormalities in alveolar nitrogen were found in 14, again indicating that the single breath test was more sensitive.

With the use of a katharometer and a closed breathing circuit, it has been possible to measure the concentration of hydrogen or helium as they became equilibrated between the spirometer and the functional residual gas of a test subject.[38, 39, 40] Knowledge of the initial and final concentration of the indicating gas and the volume of gas in the spirometer allowed for calculation of the functional residual capacity. A series of determinations of the functional

residual capacity as well as the rate at which the helium became diluted in normal and in emphysematous subjects[41] were carried out speedily and accurately with a high degree of reproducibility. Compared to normal persons, patients with pulmonary emphysema showed significant slowing in the rate at which helium was diluted. This work has been criticized because account was not taken of variation in the lung or tidal volumes among their subjects. Bates and Christie[39] suggested that mixing efficiency might be more advantageously assessed by an index derived from the ratio between the expected and the observed number of respirations needed to reach 90 per cent of mixing. Even though they made no allowance for the dead space of their apparatus or for the dead space of the patient, this index, nevertheless, gave a good separation between normal and emphysematous subjects. Among their patients was one with bronchial asthma who showed poor mixing which improved when the patient recovered. With the 90 per cent mixing index Bates,[42] in a study of 13 children with bronchial asthma, found significant abnormality in the majority.

That the delay in helium mixing could be assessed in terms of the volume of the poorly ventilated space of the lung has been proposed by another group.[40, 43] In plotting the logarithm of the falling helium concentration against time, they found that normal subjects gave a steep straight line, whereas some patients showed retardation and an inflection in the curve. From the helium concentration at the point of the inflection and the final helium concentration, a volume which they called the poorly ventilated space was calculated (Fig. 3). Likewise, it was possible to compare the rate of ventilation of the well and poorly ventilated areas of the lung. By this method only a few normal subjects had any detectable inequality in ventilation of the lungs and in none did the poorly ventilated space exceed one liter. In all of 10 asthmatic subjects[44] abnormal mixing indices were present and the volume of the poorly ventilated space averaged 1,695 c.c. Four patients restudied after the subcutaneous injection of epinephrine gave steeper, straighter curves, the poorly ventilated space decreased by 400 c.c. on the average, but none became normal.

RESPIRATORY GAS EXCHANGE

In normal individuals the inspired gas is distributed to the perfused alveoli in a very efficient manner. In bronchial asthma or emphysema and in certain other pulmonary conditions, abnormal distribution of the inspired gas may lead to underventilation of well-perfused alveolar spaces. As a result, blood leaves these spaces without becoming fully saturated and compensation can occur only if these spaces become better ventilated or less well perfused. Although normal or increased ventilation of other spaces of the lung will bring about increased elimination of carbon dioxide, oxygen will not move into the blood in larger amounts there.[45] For this reason, hypoxia frequently occurs in the absence of carbon dioxide retention. The development of retention of carbon dioxide and respiratory acidosis, both of which are seen in emphysema[46] and occasionally in uncomplicated bronchial asthma,[47, 48] depends on the degree of the abnormality in alveolar ventilation and perhaps to other factors, pulmonary or extrapulmonary, as yet unrecognized.

So far as we can determine there is no evidence for impairment of the diffusing capacity of the lungs in bronchial asthma. Methods depicting the diffusing capacity of the lungs have been reviewed in a recent article on respiratory gas exchange by Riley.[8] Recently, Bates[49] reintroduced the carbon monoxide method. In brief, a subject inspires gas with a carbon monoxide concentration of 0.115 to 0.145 per cent and the concentration in the expired gas is determined by means of an infrared analyzer. Normal subjects absorb about 53 per cent of the carbon monoxide during quiet breathing. In asthmatic subjects the carbon monoxide uptake remained normal even in the presence of impaired helium mixing as severe as that seen in emphysema.

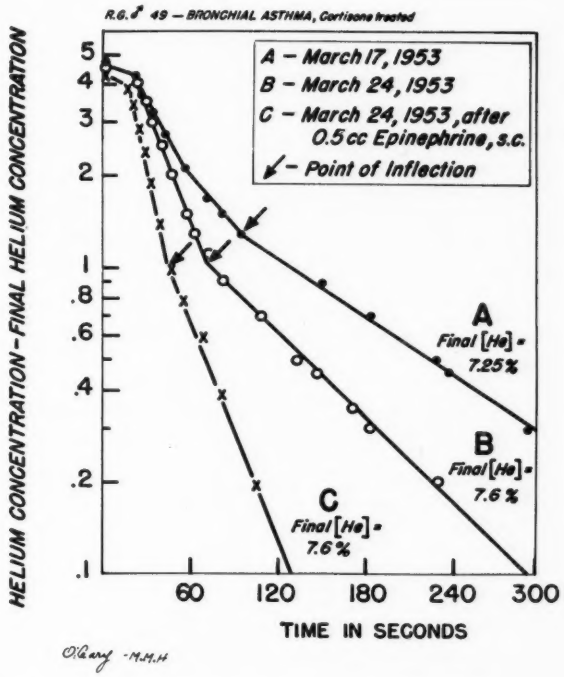

Fig. 3.—Functional residual capacity and "mixing" efficiency determined by helium dilution method. The volume of the gas in spirometer (V_s) was 6,750 c.c. with a helium concentration [He_i] which varied slightly for each run but was approximately 12.5 per cent. The curves *A*, *B*, and *C* show the manner in which the helium concentration fell during three measurements of the functional residual capacity (FRC), which may be calculated from the initial and final concentration of helium according to the formula $\frac{[He_i] - [He_f]}{[He_f]} \times Vs$ where $[He_f]$ is the final helium concentration.

The volume of the poorly ventilated space (PVS) may be calculated by substituting for $[He_f]$ the value of the helium concentration at the point of inflection. This apparent FRC is then subtracted from the FRC to give the volume of the PVS.

The results of the calculations based on the above three curves are as follows:

	A	B	C
FRC	4,235 c.c.	3,768 c.c.	3,464 c.c.
Res. Vol.*	4,023 c.c.	3,360 c.c.	2,644 c.c.
PVS	1,440 c.c.	1,208 c.c.	924 c.c.

The slope of the curves indicates the rate at which the helium is equilibrated between the spirometer and the lungs, and by inspection a rough estimation of the mixing efficiency of the lung can be obtained and this is clearly different for the three curves.

*Calculated by subtracting the expiratory reserve volme from the FRC. We are indebted to Dr. Richard Stone for carrying out the above measurements.

Study of the arterial blood gases and pH provides information of much value. In some studies, normal saturation was observed[22, 23] even in the presence of faulty distribution and mixing as determined by the open circuit method,[20] whereas in others,[21] unsaturation was present and hypercapnia was absent. Hypoxia may accompany the induced asthmatic attack[26, 50] to be discussed below.

The ventilation equivalent may be of help in estimating over-all pulmonary efficiency. Having determined the oxygen consumption and the minute volume in the usual manner, one may calculate the amount of air in liters from which the lungs remove 100 c.c. of oxygen. The normal value for this is 2.2 to 2.5 liters. Where the metabolic needs are higher as in fever, the increase in ventilation parallels the increase in oxygen consumption so that the ventilatory equivalent remains normal. On the other hand, in asthma or in certain other pulmonary diseases the ventilatory equivalent will increase in proportion to the severity of the disease. During this procedure, anxiety and discomfort may in themselves increase ventilation and lead to an erroneous interpretation.

Using the oximeter, the rate at which the saturation of the arterial blood rises upon the inhalation of 100 per cent oxygen is slowed in some patients with pulmonary disease and this may be used as an over-all test of pulmonary function.[51-54] We have used an adaptation of a method described by Fowler and Comroe,[51] and again by Douglas and Edholm,[52] and have found that normal subjects usually require 3 to 6 seconds for the arterial oxygen saturation to rise from 90 to 95 per cent. However, in patients with asthma and emphysema the time required varied from 4 to 20 seconds, the longer period being seen in patients with marked respiratory disability. This rate was readily modified in asthmatic subjects. It was accelerated by the subcutaneous injection of epinephrine or prolonged by aggravation of the asthma with aerosolized histamine.[54]

THE INDUCED ASTHMATIC ATTACK

The changes in pulmonary function which characterize asthma can be seen in their most dramatic form when measurements are made during the purposeful induction of an asthmatic attack.[50, 55-57] These changes often occur to a significant degree even though only mild or moderate symptoms occur, and on numerous occasions clear-cut and characteristic changes have been induced in patients who had sensations described by them as mere forerunners of an attack. This indicates that tests of pulmonary function are very sensitive indices of asthma.

In suitable subjects asthmatic attacks may be induced by the injection, intravenous or intramuscular, of histamine or acetyl-beta-methylcholine or by inhalation of aerosolized solutions of these drugs or an allergen.

As one might expect from the experience in spontaneous asthma, the induced attack is characterized by a decrease in the vital capacity and its fractions, an increase in the functional residual capacity, and there may also be a fall in arterial saturation and a prolongation in the saturation rate.[26, 50, 54, 58, 59]

All these changes may be quickly reversed, wholly or in part, by the administration of bronchodilator drugs. A reduction in minute volume may occur in severe attacks, to be followed shortly by an increase beyond the intital level.[26, 54]

EQUIPMENT AND PROCEDURES FOR PULMONARY FUNCTION STUDIES

The equipment required for performance of tests of pulmonary function depends a good deal on how far such tests are to be carried. If the purpose is simply to make a rough estimate of the degree of the respiratory obstruction whether from bronchial asthma, pulmonary emphysema, or a combination of the two, the needed information may be obtained with what may be called the "open" method. This consists of a spirometer and a timing device, the most satisfactory of which appears to us to be a rapidly-moving kymograph. This gives a record of the speed of air flow throughout the expiratory effort. The need for a timing device arises from the fact that the greatest functional impairment in bronchial asthma and emphysema appears to be obstructive in nature rather than the extent to which the lungs can be inflated and deflated. Speed of air flow is therefore an important key to the patient's disability. More compact and less cumbersome but also less informative is a timing device* which may be attached to a spirometer permitting measurement of the volume expired in the first or subsequent seconds during the performance of the vital capacity.[30]

The patient, having been instructed to make a maximal inspiration, blows into a large bore tube leading to the spirometer. If a kymograph is used, this must be set in motion *before* the patient begins to blow out, or gross errors in timing will occur. The patient should continue to blow out forcibly until no further air will leave the chest. Cough occurring during the expiratory effort may interfere with timing but a satisfactory measurement of the vital capacity can often be obtained. A noseclip is usually unnecessary. In some patients repeated measurements of the vital capacity, especially if asthma is present and if measurements are made at short intervals (less than 1½ minutes), may lead to a progressive fall in vital capacity and the appearance or aggravation of respiratory symptoms. This should always be taken into account in any procedure designed to decrease the vital capacity either as a diagnostic or investigative procedure. As a rule, this will not occur in asthmatic patients who are free of symptoms. Tests carried out at intervals during the course of the patient's illness will give much more information than measurements made on any single day.

The vital capacity is usually expressed both as the volume expired and as the per cent of the predicted normal for the age and sex of the patient. The rate of expiration is, for most purposes, adequately expressed as either the per cent of the total expired in the first second[30] or perhaps preferably as a per cent of the volume that a normal person would be expected to expire in the same interval. This figure is very markedly decreased in both bronchial asthma and pulmonary emphysema. The effect of a bronchodilator drug such as isopropyl-

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arterenol by nebulizer may give a clue as to the nature and degree of the pulmonary disease. In patients with mild or moderately severe asthma, both the vital capacity and the rate of expiration will often increase markedly.[30, 58, 59, 60] In other words, lability is characteristic of bronchial asthma. To be sure, some patients with severe protracted asthma will show relatively little change but will exhibit this lability at other times when the asthma is less severe.[61] On the other hand, patients with emphysema show less response to bronchodilator drugs and their pulmonary disease tends to be relatively fixed.

If the vital capacity is performed *rapidly* and then a minute or two later is performed *slowly,* the second will often significantly exceed the first. This is characteristic of patients with either asthma or emphysema and suggests that uneven distribution of the inspired air is also present (Fig. 2).

The use of the "open" method for the measurement of the vital capacity and the expiratory rate leaves out certain other aspects of the spirogram which are often worth measuring. These consist of the expiratory reserve volume and the inspiratory capacity. For these a so-called "closed" system is required. A spirometer of the Benedict-Roth type, often used for determination of the metabolic rate, is satisfactory. We have found it advantageous and time-saving to connect the spirometer bell with two writing pens, one which records on paper driven continuously by a slow kymograph and the other on paper driven intermittently by a fast kymograph. With this arrangement, accurate timing of the vital capacity can be obtained when this measurement is made as part of the usual spirogram.

If, instead of a rebreathing apparatus of the Benedict-Roth type a two-compartmented space of 100 liters or more is used as a reservoir of gas,[26, 62] then any desired gas mixture of unchanging composition may be administered at will. A volume of 100 liters is sufficient for about ten minutes of quiet respiration. In this arrangement there is no rebreathing and, as air flow is always in one direction, the apparatus is bacteriologically clean. All the procedures mentioned in the preceding paragraph may readily be carried out with this apparatus, air may be used, and there will be no need for a carbon-dioxide scrubber or the addition of oxygen to replace that consumed by the subject. If a pair of such reservoirs is connected with appropriate valves, two gases may be administered in rapid succession. It also becomes a simple matter to detect and measure the reduction in minute volume commonly seen in patients with chronic pulmonary disease and arterial unsaturation when an abrupt change from air to oxygen is made.[13, 26, 46, 63]

Neither of the previously mentioned closed systems is ideally adapted for the determination of the maximal breathing capacity. The inertia of a spirometer, the tendency of the water within it to oscillate, and the resistance of the tubing make for errors, especially in patients who have relatively normal lungs. In the effort to streamline the conventional spirometer for this purpose by removal of the carbon-dioxide scrubber, the questionable standard of cleanliness of the apparatus is further lowered. If the maximal breathing capacity is to be determined, then a Douglas bag or a large capacity spirometer (Tissot) should

be used for collection of the expired gas. Furthermore, a very low resistance valve and mouthpiece assembly are required. The collected gas is measured and the time of maximal expiratory effort carefully determined with a stop watch. We have found this procedure to be impractical in asthmatic patients for the following reasons: (1) the respiratory effort tends to aggravate the patient's symptoms; (2) in sick patients the effort involved is fatiguing or exhausting, especially as the determination demands *maximal sustained effort;* (3) in sick patients a second determination, often required as a check or for other reasons, either cannot be done or the second effort is not maximal. Equally valuable information may be obtained by other means, the simplest of which appears to be a tracing on a high-speed kymograph of a maximal expiratory effort. For these reasons, we do not carry out determinations of the maximal breathing capacity in this laboratory, where the primary interest is bronchial asthma.

In most instances the previously mentioned procedures yield adequate information for clinical purposes in patients with bronchial asthma. However, in addition to the residual volume, more can be learned as to the nature and the degree of the functional defect by application of methods designed to determine the manner in which the inspired air is distributed within the lung and the efficiency with which the inspired gas is exchanged with that in the alveolar spaces. Pulmonary or intrapulmonary mixing is commonly used as a brief term for this but with some sacrifice of precision. Of the available methods the most practical from the point of view of expense and the required technical skill is the helium dilution method from which, in addition to the measurement of the functional residual capacity from which the residual volume and the total lung capacity can be derived, an estimate of the rate of intrapulmonary exchange of gas and the volume of spaces in the lung which are poorly ventilated can be determined (legend, Fig. 3).[39, 40] Very little cooperation and no sustained effort is required of the patient during these determinations, all of which may be calculated from a single "run."

To take full advantage of those techniques which are within reasonable reach of the clinician who plans both to assess the magnitude of the defect in pulmonary function and to engage in differential diagnosis of diseases with respiratory manifestations, arterial puncture, and the determination of the oxygen saturation, the pH, the carbon-dioxide content and the pCO_2 of the arterial blood should be included. For the first, a Van Slyke apparatus is required or a suitable spectrophotometer[64, 65]; for the second, a pH meter of the potentiometer type equipped with a specially designed electrode for blood*; the pCO_2 may be calculated from the pH and the carbon-dioxide content of the arterial plasma or serum (not whole blood). By these means, unsaturation and respiratory acidosis can be recognized and accurately assessed. As an alternative to this, but less satisfactory, is the use of the oximeter for the measurement of arterial oxygen saturation[66] and a venous blood sample for the determination of pH and carbon dioxide. The venous blood should be obtained without

*Cambridge Instrument Co., Grand Central Terminal, New York, N. Y.

stasis. At its present stage of development, the oximeter, though well-adapted for detecting rapid changes in saturation, is not very suitable for absolute determinations of arterial oxygen saturation.

SUMMARY

Methods for the study of pulmonary function have been applied by a number of workers in patients with bronchial asthma and have gone far to elucidate the changes which occur during the asthmatic attack. Although valuable information concerning the severity of asthma can usually be obtained with a spirometer, coupled with measurements designed to assess the obstruction to air flow, a much deeper understanding of the functional defect can be derived from tests which also measure abnormalities of distribution of the inspired gas, and the changes which occur in the arterial blood.

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Editorial

INSTITUTIONS FOR THE CARE OF ASTHMA

DESPITE the progress and innovations in the treatment of asthma during the past fifty years, one of the oldest approaches to the problem, the change of climate, remains popular with physicians and patients. Osler recommended Egypt as an ideal winter climate for the asthmatic patient, today Arizona is more often suggested, but the principle of a warm dry climate remains the same. While climatotherapy, like most other methods of treating asthma, falls far short of universal efficacy, such persistent popularity must have a basis of fact. With better understanding of the causative factors in asthma, it is possible to predict with greater success which patients need and may be expected to benefit from a change of climate, particularly those whose asthma results in a large part from chronic or recurrent respiratory infections. In other cases where the symptoms result from allergy to occupational or household contacts, the details of the environment are more important than the geographic location. Not infrequently, the change of climate is prompted by desperation rather than logic, on the part of the patient, his physician, or both, after other measures have failed to produce relief. Regardless of the care of selection, however, not all do well in their new locations.

For the average patient a permanent change of climate requires a formidable economic adjustment, and if the benefits are not satisfactory, the results may be tragic. The type of asthma which justifies such a radical step is difficult enough to control at home with established medical connections, but if it must be faced in a strange locality, without knowledge of the local medical facilities and with depleted financial resources, the problem becomes desperate.

There is a real need for facilities for the care of asthmatic patients of limited means in the areas of good climatic conditions, so that patients making a change of climate may do so, preferably at first on a trial basis, with assurance of a reasonable period of rest and care while adjusting to their new environment. Obviously such institutions need national support; it would be unreasonable to expect a few states to undertake the care of asthmatic patients from the rest of the country in public or locally supported charitable institutions.

In the past such facilities have been provided for the care of a limited number of children. The Jewish National Home for Asthmatic Children at Denver has done excellent work in this field for a number of years. More recently the National Foundation for Asthmatic Children in Tucson has provided a place for children of families of limited means from other parts of the country. The first offer of such accommodations for adult patients is being made by the Ex-Patients' Sanatorium for Tuberculosis and Chronic Disease at Denver. While these facilities are at present limited and the altitude of Denver may present a problem in some cases, they represent a worthy beginning of a program for rehabilitation of the more difficult cases of asthma. It is to be hoped that improved methods of treating tuberculosis may free more facilities now devoted to the care of that illness for the treatment of asthma. The present facilities deserve the support of all those interested in the care of asthmatic patients and set a precedent which may well be followed by the American Foundation for Allergic Diseases.

American Academy of Allergy

REAGINIC SERUM BANK

THE reaginic serum bank, an integral part of the Research Council of The American Academy of Allergy, is urgently in need of reaginic sera of high titer to the foods, particularly to the fruits and leafy vegetables. These sera are needed to test allergenic extracts prepared by different methods. The validity of our results will, in part, be proportional to the number of sera available for experimentation.

We are asking all Academy Members to aid in this endeavor.

If you have a patient who is extremely sensitive to any of the foods, will you be good enough to draw 40-50 c.c. of blood and forward it to Dr. B. Siegal, care of Brooklyn Jewish Hospital, 555 Prospect Place, Brooklyn, New York. Special mailing cartons and handling instructions may be obtained in advance from the same source.

Your cooperation is urgently requested.

Announcements

American Foundation for Allergic Diseases

Formation of a Scientific and Educational Council of nationally known scientists end educators to promote more research and wider professional education in the field of the allergic diseases has been announced by the American Foundation for Allergic Diseases from national headquarters, 525 Lexington Avenue, New York City.

The members are as follows: Robert A. Cooke, M.D., Director, The Institute of Allergy, Roosevelt Hospital, New York; Frank J. Dixon, M.D., Professor of Pathology, University of Pittsburgh Medical School, Pittsburgh, Pa.; Alfred Gilman, Ph.D., Professor of Pharmacology, College of Physicians and Surgeons, Columbia University, New York; Elvin A. Kabat, Ph.D., Professor of Microbiology, College of Physicians and Surgeons, Columbia University, New York; Richard A. Kern, M.D., Professor of Medicine, Temple University Medical School, Philadelphia, Pa.; Giles A. Koelsche, M.D., Assistant Professor of Medicine, Mayo Foundation Graduate School, University of Minnesota, Rochester, Minn.; John H. Mitchell, M.D., Professor of Clinical Medicine, Ohio State University, Columbus, Ohio; Henry Stevens, Ph.D., head of Section on Allergens, Agricultural Research Service, U. S. Department of Agriculture, Washington, D. C.; Cyrus C. Sturgis, M.D., Director, Simpson Memorial Institute for Medical Research, Professor of Medicine, University of Michigan, Ann Arbor, Mich.; Marion B. Sulzberger, M.D., Chairman, Department of Dermatology and Syphilology, Post-Graduate Medical School, New York University-Bellevue Medical Center, New York.

The American Foundation for Allergic Diseases was established a year ago under the sponsorship of the American Academy of Allergy and the American College of Allergists as a nonprofit organization of physicians and laymen to promote allergy research, improve professional education, increase treatment facilities for allergy sufferers, and spread public understanding of the allergic diseases so as to bring about early diagnosis and treatment.

The Academy of Psychosomatic Medicine

The program of the first annual meeting of the Academy of Psychosomatic Medicine, to be held at the Plaza Hotel in New York City on Oct. 8-9, 1954, will be devoted to Psychosomatic Aspects of Surgery. There will be contributed and invited papers on such topics as: Psychosomatic Aspects of Anesthesia; General Surgery; Gynecological Surgery; Plastic, Otolaryngological and Oral Surgery; Mutilating Operations; Endoscopic Surgery; Orthopedic Surgery; Eye Surgery; Pediatric and Geriatric Surgery; and Neurological Surgery.

Those who are interested in presenting papers should write to Dr. Benjamin Raginsky, 376 Redfern Ave., Montreal, Canada, stating their special interest.

The Academy of Psychosomatic Medicine is still receiving applications for fellowships and associateships, according to Dr. Ethan Allan Brown, Secretary, 75 Bay State Rd., Boston 15, Massachusetts. New fellows will be inducted into the Academy at the October meeting in New York City, at which time certificates of membership will be presented.

Meeting of the Swiss Society of Allergy

A Meeting of the Swiss Society of Allergy was held May 20, 1954, at Zurich. The present officers of this society are W. Jadassohn, Chairman, and Dr. J. Mozer, Secretary, both of the University of Geneva.

Annual Meeting of the British Association of Allergists

The Annual Meeting of the British Association of Allergists was held July 3, 1954, at Leicester, England. Dr. Leslie N. Gay of Johns Hopkins, presented a paper on "The Treatment of the Ambulatory Asthmatic with ACTH."

The current officers of the association are:

President Dr. R. S. Bruce Pearson, D.M., F.R.C.P., Affiliate Fellow of the Academy.

Vice-President Dr. D. A. Williams, M.D., M.R.C.P., Affiliate Fellow of the Academy.

Secretary Dr. A. W. Frankland, Affiliate Fellow of the Academy.

Treasurer Dr. C. J. C. Britton, Affiliate Fellow of the Academy.

Members of the Council:

Dr. C. A. Clarke
Dr. J. Overton
Dr. J. Peys
Dr. A. W. Thrower
Dr. C. H. Whittle
Dr. K. Mannsell
Dr. D. Blair Macauley
Dr. V. B. Walker

Honorary Members:

Sir Henry Dale
Dr. John Freeman
Prof. J. S. McDowall

Correspondence

N. Y., March 22, 1954

To the Editor:

This is in response to the letter of Dr. Michael Schwartz (J. ALLERGY **25**: 90, 1954) relative to the inheritance of allergy. We welcome the discussion that our paper (J. ALLERGY **24**: 371, 1953) has evoked.

Dr. Schwartz questions our lack of description of the criteria. The criteria were discussed in a previous communication (Ann. Allergy **10**: 1, 1952). Unfortunately, Dr. Schwartz ignored this reference to our earlier paper in which the criteria were spelled out in detail.

We question the propriety of Dr. Schwartz's deletion of the 250 patients from our families since they are a part of the so-called allergic population. This deletion is an arbitrary selective exclusion on his part, thus reducing the 9.8 per cent incidence of allergy we obtained in the allergic population to 6.1 per cent.

In our paper, in Table III, appears a breakdown of the families of the 250 allergic children. The groups most closely comparable to the 3,000 in the random population we studied, are the parents and siblings of our patients. These were questioned firsthand in the identical manner as were the previously mentioned 3,000 individuals. Of a total of 840 (parents and siblings of the 250 allergic patients), 89, or 10.6 per cent, were allergic. We obtained 7.1 per cent in the grandparents and 4.9 per cent in the collateral members. Therefore, the 6.1 per cent is the incidence in the family members of the allergic children. However, the 250 allergic patients belong to the allergic family constellation which Schwartz does not seem to realize. His 6.1 per cent represents an unreliable figure obtained from partial data and is the pitfall into which so many have fallen.

Neither side can be entirely right or entirely wrong. It is with regret that we had to criticize the monograph of Dr. Michael Schwartz (*Heredity in Bronchial Asthma*, Copenhagen, 1952, Munksgaard).

Dr. Schwartz has failed to demonstrate the hereditary factor. Actually he failed to find this factor in certain allergic states such as eczema, and he arbitrarily decided that they were not true allergies. This is contrary to the entire body of clinical and immunologic experience.

An analysis of all the literature shows a negative family history in approximately 50 per cent of allergic individuals. We found that in only a small percentage of families of allergics is there a high incidence of allergy. The data obtained by the proponents of the hereditary concept gave the same evidence. The fact of the matter is that allergy is not more prevalent in the family of the allergic than in the nonallergic.

We stated in our paper, "An evaluation of the available data does not satisfactorily demonstrate that within the scope of the antigen-antibody mechanism, the capacity to become sensitized is controlled by genetic influences." We do not say that heredity does not play any role in allergy; we merely state that this factor has not been demonstrated.

Sincerely yours,

Bret Ratner, M.D.

David E. Silberman, M.D.

Book Reviews

The Allergic Child. By Harry Swartz, M.D. New York. Coward-McCann, Inc., 1954, 285 pages. Price, $3.95.

Dr. Swartz has done a good job. He has presented a difficult subject and a good deal of information in a concise and lucid form which the intelligent layman should be able to comprehend. The book is a small one, and the author has wisely chosen not to get involved in controversial points of view. In this way, however, he does lay himself open to criticism. It may be true that food binges of the pregnant mother may be the underlying cause of sensitization of the infant to a particular food in certain instances. The restriction of the diet of the pregnant mother, however, with respect to milk and eggs, in order to prevent the subsequent development of hypersensitivity to these substances in the newborn infant is a concept and a recommendation on which there is certainly difference of opinion.

The organization of the book is logical and clear. Beginning with an excellent chapter devoted to a discussion of the emotional maturation of the child within the parental framework, the author goes on to an outline of the physiologic and pharmacologic change associated with the allergic state. The clinical manifestations of hypersensitivity are briefly but adequately presented as are the complications of allergic conditions. There is a good discussion of the relationship of emotion and the allergic state. Certainly it seems wise to point out, as the author has done, that an allergic syndrome in a child does not mean that the parents have been remiss in their duties. It is important for the parents to be aware of the fact that alleviation of symptoms due to hypersensitivity may be associated with improvement not only in the child's physical state but behavior and mental attitudes as well.

Parents are often unwilling to subject their children to the "needles" which they invariably associate with a visit to the allergist. Dr. Swartz's discussion of the technique of investigation of this problem discussed in a chapter, "How the Doctor Handles the Allergic Child," should help to eliminate the anxiety felt by parents. It should also serve to make this type of study more acceptable to them so that they do not wait too long for the child to "outgrow" his condition, or until symptoms have reached the stage where the child has become seriously ill. Other common misinformation is discussed in a chapter on "Myths About Allergy."

Implied in the author's presentation are the qualifications of the pediatric allergist as a man aware of the child as a whole and not only of his hypersensitivities. These must be evaluated in their true perspective and as part of a total personality picture. He must also be aware of the normal variations in the growth and development of the child and know when help from other sources is needed.

The appendix contains a good deal of data on food, the composition of various trade preparations, and data which should prove helpful in planning children's diets.

In short Dr. Swartz has written a stimulating and informative book for parents and one the physician can read with pleasure.

W. R. K.

Current Therapy 1954. Edited by Howard F. Conn, M.D., Philadelphia and London, W. B. Saunders Co., 1954, 898 pages.

This large volume, published annually, represents the combined efforts of twelve consulting editors and several hundred contributors. It furnishes the practitioner with a quick reference to indicate what is new in therapy, and what is still standing the test of time. In general, well-rounded programs of treatment are offered without undue stress on the most recent innovations. No doubt the volume as a whole should be useful to those physicians who devote a majority of their time to allergy and may have failed to keep abreast of progress in other fields of medicine. Conversely, the section on allergic diseases offers useful advice to the practitioner with limited experience in this field.

In the section on allergy, a number of new contributors have given a broader coverage of the field, but otherwise the annual revision reveals little that is actually new over the past year or two. Corticotropin and cortisone are given a somewhat more prominent place in the treatment of allergic diseases and stated to be lifesaving to many asthmatics. On the other hand, the reader is reminded that they are still very expensive. Can this be in relation to the cost of days in the hospital or time lost from work? One is surprised to read that cortisone and corticotropin must be continued for at least several weeks once they are started for the treatment of asthma.

The chief weakness of this book is in the lack of adequate editing. While the contributors are selected as recognized authorities in their respective fields, they are not above the human failings of using proprietary names of drugs whose official names are equally or even more familiar, introducing such irrevelant statements as that Wesley Memorial Hospital in Chicago has 12 beds especially fitted for severe asthmatics, and, worst of all, misplacing decimal points in dosages of drugs. The presence of four such dosage errors on a single page describing the treatment of asthma (epinephrine 1:1,000 *0.03* c.c. by injection, ephedrine to *0.5* gram, and aminophylline *0.025* gram to *0.05* gram intravenously) is enough to destroy confidence in all dosages given in the book. It is regrettable that such errors are present in a volume to which so many distinguished men have contributed so much excellent material.

Immunity, Hypersensitivity, Serology. By Sidney Raffel, Sc.D., M.D., New York, Appleton-Century-Croft, Inc., 1953, 531 pages.

Despite the tendency of antibiotics to replace sera in the therapy of infectious diseases, recent years have seen many important developments in the field of immunology, such as new knowledge of resistance to virus, innumerable new blood group factors, and evidence of hormonal influences on antibody formation. During this period, few new books on the subjects have appeared, so that a fresh and clear exposition of the subject, integrating these and other new concepts is most welcome to the student and physician. Dr. Raffel has furnished such a book.

The quantitative chemical analysis of the antigen-antibody reaction receives only brief mention in line with the author's attempt to deal with circulating antibody in relation to the actual resistance to infection, and not let the highly developed knowledge of this most conveniently accessible manifestation of the immune reaction overshadow the entire subject. In his words, "This distortion is at best a case of the tail wagging the dog, and at worst in the many instances where a relationship of antibodies to immunity has not been established—a case of dog being wagged purely by wishful thinking."

Those whose primary interest is in allergy will find an excellent summary of its theoretical background in a section comprising eighty pages and backed by a remarkably complete bibliography. The known facts are clearly presented, the gaps in our knowledge recognized, and alternative hypotheses offered without straining to fit the whole into a preconceived concept. Noting that "the chief factors which influence the nature

of the antibody response are the species of animal which produces the antibody, the antigen employed, the route by which antigen is administered, and the duration and intensity of the vaccinating procedure,'' the author records the obvious similarities and equally obvious differences between clinical allergy and experimental anaphylaxis without the efforts to establish or disprove their identity that have been the keynote of so many previous writings on the subject. The discussion of the relationship of hypersensitivity to immunity to bacterial infection is also excellent, analyzing various organisms in terms of the specific antigens producing protective antibodies and those producing hypersensitivity, rather than dealing in the generalizations used by many other authorities on the subject.

On the whole, the book appears to be one of the best available in the subject and is strongly recommended.